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**ACL INJURY AND SURGERY: ASPECTS ON FUNCTION,
MUSCULAR MORPHOMETRY AND EFFUSION**

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ACL injury and surgery: Aspects on function, muscular morphometry and effusion

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It is my hope that every practitioner who reads this book shall be enlightened and inspired to further their knowledge and use their creativity in maintaining best possible practice of pre- and rehabilitation.

ABSTRACT

Background: ACL injury and reconstructive surgery, globally and in Sweden, has an established orthopedic treatment course. Reconstruction usually is performed on indication of knee instability after attempting an intensive course of rehabilitation. In some occasions reconstruction is performed on indications of the work- or athletic demands on the individual knee. Physical activity levels may vary widely between people in need of ACL reconstruction (ACLR), but injured people in need of surgery have in common after injury and rehabilitation that they cannot optimally function at their desired activity level. Rehabilitation strategies after both injury and surgery aim to restore strength and function to the fullest. Every-day normal, simple functions like gait may in the long run suffer from the consequences of the joint trauma, effusion and diminished muscular capacity. Years of strength and function deficits can be detrimental. The research covered in the spectrum of this thesis investigates gait adaptations after injury, thigh muscle cross-sectional area and its associations to various outcome variables as a consequence of injury and surgery, and knee joint effusion factors associated with injury and surgery.

Aim: In order to comprehensively analyze effects of ACL injury and reconstructive surgery the investigations had the following aim:

- To compare gait patterns of chronic ACL injured subjects with healthy control subjects (study I).
- To analyze changes in muscular morphometry before and one year after ACL reconstruction and relate changes over one year to outcome variables one year after ACL reconstruction (study II and III).
- To analyze presence and effects of knee joint effusion before and three months after ACL reconstruction, and to investigate if postoperative brace regime affects presence of effusion (study IV).
- To analyze if a postoperative brace affects general outcome one year after ACL surgery with hamstring graft (study III and IV).

Methods: Three-dimensional gait analysis and electromyography (EMG) was used to study gait parameters and muscle activity-patterns of non-operated ACL copers, who had been injured for at least one year, and of a control group. In another cross-sectional study, ACL-injured who were scheduled for ACL reconstruction were examined with computed tomography (CT) to analyze thigh muscle cross-sectional area (CSA) of the quadriceps, semitendinosus, semimembranosus, biceps femoris, gracilis and sartorius muscles. A randomized controlled trial was then initiated with ACL injured and subsequently reconstructed patients. These patients were randomized into two groups with a postoperative treatment alternative with or without a brace for the three initial weeks after surgery. A group of the randomized subjects were included in a prospective investigation on the effects of injury and surgery on muscular morphometry (CSA) before and one year after surgery. The randomized controlled trial investigated effects of injury and surgery on presence of effusion

before and three months after surgery as detected by computed tomography (CT). Clinical, subjective and functional parameters, before and one year after surgery, were correlated to the findings.

Main results: Results show that ACL injured copers, although functioning at above normal activity level, display aberrant muscular activity patterns in gait, but that gait parameters are otherwise similar to controls.

ACL injured subjects scheduled for ACL reconstruction show quadriceps CSA ratio deficits of the injured leg, which are comparably larger when the right knee is injured. Women have preoperative hypotrophy of semimembranosus. Thus, effect of ACL injury on muscle size differs between left- and right-sided injuries and sex.

ACLR subjects show unchanged quadriceps CSA ratio deficits of the reconstructed leg at the postoperative one-year follow-up. These subjects also show gender-specific patterns of biceps femoris and semimembranosus muscular hypo- and hypertrophy over time before to after surgery.

There is no effect of a postoperative brace on any of the investigated clinical, subjective and function or CT effusion parameters. Predictors of presence of knee effusion at three months after ACL reconstruction are a prior meniscus injury, higher Tegner activity level before the injury and a higher Lysholm score at baseline/ before surgery.

Conclusion: This thesis provides results from investigations closely related to function and rehabilitation: Long time ACL injured subjects display aberrant muscular activity patterns in gait. Women and men have a different response to the ACL injury and subsequent surgery regarding muscular morphometry effects, i.e. muscular CSA, before and after ACLR. The effect of ACL injury may also differ for the right and left limb. Prior meniscus injury may delay knee joint homeostasis, with regards to presence of effusion, after initial injury as well as after ACLR. A postoperative brace is not necessary after ACL surgery with semitendinosus-gracilis (ST/G) graft, since no associations can be found which affect presence of effusion at three months and thus improved knee homeostasis, nor regarding clinical and functional variables at one year after surgery.

LIST OF SCIENTIFIC PAPERS

- I. Lindström Maria, Felländer-Tsai Li, Wredmark Torsten, Henriksson Marketta. Adaptations of gait and muscle activation in chronic ACL deficiency. *Knee Surg Sports Traumatol Arthrosc.* 2010 Jan;18(1):106-14. doi: 10.1007/s00167-009-0886-x. Epub 2009 Aug 20. Reprinted with the permission from the publisher.
- II. Strandberg S, Lindström M, Wretling ML, Aspelin P, Shalabi A. Muscle morphometric effect of anterior cruciate ligament injury measured by computed tomography: aspects on using non-injured leg as control. *BMC Musculoskelet Disord.* 2013 Apr 29;14:150. doi: 10.1186/1471-2474-14-150. Reprinted with the permission from the publisher.
- III. Lindström Maria, Strandberg Sören, Wredmark Torsten, Felländer-Tsai Li, Henriksson Marketta. Functional and muscle morphometric effects of ACL reconstruction. A prospective CT study with 1 year follow-up. *Scand J Med Sci Sports.* 2013 Aug;23(4):431-42. doi: 10.1111/j.1600-0838.2011.01417.x. Epub 2011 Nov 23. Reprinted with the permission from the publisher.
- IV. Lindström Maria, Wredmark Torsten, Wretling Marie-Louise, Henriksson Marketta, Felländer-Tsai Li. Postoperative bracing after ACL reconstruction has no effect on knee joint effusion. A prospective, randomized study. *Knee.* 2015 Dec;22(6):559-64. doi: 10.1016/j.knee.2015.04.015. Epub 2015 Jun 6. Reprinted with the permission from the publisher.

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LIST OF ABBREVIATIONS

ACL	Anterior cruciate ligament
ACLD	Anterior cruciate ligament deficient
ACLR	Anterior cruciate ligament reconstruction
AMI	Arthrogenic muscular inhibition
CSA	Cross-sectional area
CT	Computed tomography
EMG	Electromyography
MRI	Magnetic resonance imaging
HU	Hounsfield units
OA	Osteoarthritis
PT	Patella tendon
ST	Semitendinosus
ST/G	Semitendinosus-gracilis

1 INTRODUCTION

1.1 ACL INJURY AND SURGERY – GENERAL BACKGROUND OF THESIS

Anterior cruciate ligament (ACL) injury in Sweden occurs at an incidence rate of 78/ 100 000 (Nordenvall et al., 2012) to 81/ 100 000 (Frobell et al., 2009) inhabitants per year, and almost 40% of those who become injured undergo reconstructive surgery (Nordenvall et al., 2012). According to the Swedish National ACL Register (2015) about 3500 patients per year undergo primary ACL reconstructive surgery in Sweden, compared to 125 000 to 200 000 patients per year in the U.S. (Noyes & Barber-Westin, 2014). In Sweden, the preferred graft choice for ACL reconstruction is hamstring tendons, dominating at 95% in 2012 (Kvist, Kartus, Karlsson, & Forssblad, 2014). At present, about half of all men and one third of all women who undergo surgery in Sweden were injured playing soccer (Ahldén et al., 2012), which is the most common activity in Sweden to cause ACL injuries for both men and women. Floorball is the second most common activity to cause ACL injury for men. For women, alpine skiing is the second most common activity to cause ACL injury, and together with European handball it is the primary activity responsible for ACL injury and surgery for more women than men, according to annual reports (Swedish National ACL Register, 2015). Females in general are at higher risk for ACL injury (Hewett, Myer, & Ford, 2006; Renstrom et al., 2008). About 70% of all ACL injuries happen in non-contact situations (Boden, Dean, Feagin, & Garrett, 2000; Griffin et al., 2000). Higher numbers of non-contact injuries are reported by for field- and court sports such as team handball with 89-95% (Myklebust, Maehlum, Engebretsen, Strand, & Solheim, 1997; Myklebust, Maehlum, Holm, & Bahr, 1998) and for males in professional soccer with 85% (Walden et al., 2015). Indication for surgery arises when knee instability limits work, leisure or sports activity, despite proper attempts of rehabilitation. Goals of surgery and subsequent rehabilitation are to achieve stability of the joint, where objective knee function and strength as well as patient subjective measures provides the outcome.

Anatomy, mechanism of injury, diagnostic tests

The ACL inserts distally in the medial/ anterior part of the tibial plateau. The two bundles that make up the ligament, the anteromedial and posterolateral are named by where they attach distally, on the tibial plateau, in relation to one another and as described by their names. Proximally, the bundles attach medially/ posteriorly on the lateral femoral condyle. Mechanism of injury occurs mostly when the knee is rotated or the body is twisted, with the foot planted. A combination of valgus force is most common, which happens frequently in decelerations, pivoting and quick changes of direction or of body mass (Boden et al., 2000; Olsen, Myklebust, Engebretsen, & Bahr, 2004). If the knee is in extension, the posterolateral bundle is taut. The anteromedial bundle is taut in about 20 degrees of flexion, to a maximum at about 45 - 60 degrees of flexion (Chhabra et al., 2006; Ferretti, Monaco, Labianca, De Carli, & Conteduca, 2008; Gabriel, Wong, Woo, Yagi, & Debski, 2004; Samuelsson et al., 2013). Magnetic resonance imaging (MRI) has demonstrated high accuracy of about 85% in

diagnosing ACL rupture when using arthroscopic verification (Crawford, Walley, Bridgman, & Maffulli, 2007; Kostov, Stojmenski, & Kostova, 2014; Prins, 2006). The Lachman test and the Pivot shift test are the most frequently used diagnostic test, where the Lachman is the most sensitive and the Pivot shift the most specific test (Prins, 2006). Thus, the Lachman test is probably more likely to give a negative result when there is not a rupture. The pivot shift is probably the more likely one to test positive when there is a rupture of the ACL.

Incidence of combined meniscus injury

Roughly 50% of ACL-injuries are combined meniscus injuries (Ageberg, Forssblad, Herbertsson, & Roos, 2010; Chen et al., 2013; Fetzer et al., 2009; Olsson, Isacson, Englund, & Frobell, 2016). One study with a very large study sample showed that different sports activities pose different risks for concomitant meniscus- and other injuries (Granán, Inacio, Maletis, Funahashi, & Engebretsen, 2013). Basketball accounted for the largest amount, 64%, of concomitant meniscus injuries, reported at the time of ACLR. Data in the study was self-reported.

Incidence of meniscus injury is reported to increase over time in the ACLD knee (Bellabarba, Bush-Joseph, & Bach, 1997; Brambilla et al., 2015; Chhadia et al., 2011; Ghodadra et al., 2013; Sri-Ram, Salmon, Pinczewski, & Roe, 2013). Due to the findings of this highly increased meniscus- and cartilage injury (second injury pathology) a debate of the timing of ACLR surgery has stirred up. Some authors have gone as far as to recommend that ACLR not be delayed more than 5 months in order to protect from further meniscus injury (Sri-Ram et al., 2013).

Incidence of future OA

ACL injury, even without meniscal damage, is proven to cause a severe trauma to the joint surface. Bone bruises and joint fluid can be observed up to one year after the trauma (Frobell et al., 2009). In long term follow-up, 13 - 16% of ACL injured with an isolated injury develop osteoarthritis, regardless if treated conservatively or with ACLR, but with combined injuries the numbers may be as high as about 50%, as concluded in systematic reviews (Claes, Hermie, Verdonk, Bellemans, & Verdonk, 2013; Culvenor, Cook, Collins, & Crossley, 2013; Øiestad, Engebretsen, Storheim, & Risberg, 2009).

Graft choice of patella tendon (PT) or hamstring does not influence future osteoarthritis (OA) in mid-term follow-up at 5 years according to a systematic review 2011 (Magnussen, Carey, & Spindler, 2011). The authors found that there was a potential for the PT graft to be associated with an increase in OA, but larger samples are needed for comparison. In a more recent review (van Meer et al., 2015) the authors conclude that limited evidence precludes that OA development could be related to graft type. Øiestad (2009) points out, in agreement with other reviewing authors (Fu & Lin, 2013; Lohmander, Englund, Dahl, & Roos, 2007) that the overall methodological quality of the available studies generally is low, and studies are heterogeneous regarding patient activity level, surgery type and the radiographic scoring

system which makes comparisons difficult. Lohmander (2007) also points out the importance of coupling findings of radiographic OA to clinically relevant findings of function, activity level or OA symptoms.

Chondral injuries are reported to be present in about 16 - 46% of acute ACL injuries (Brophy, Zeltser, Wright, & Flanigan, 2010). In a more recent systematic review (van Meer et al., 2015) the authors state that conflicting evidence exists whether chondral injuries may predict future OA after ACL injury or reconstruction. In another recent systematic review (Filardo et al., 2016) the authors conclude that chondral lesions provide poorer subjective, objective and radiographic outcome after ACLR. Like meniscal injuries, chondral lesions seem to be more frequent in ACL injured with longer time to ACLR. A recent study of 988 subjects investigated if the time to surgery was associated with number of knees with chondral lesions (Brambilla et al., 2015). The authors found a greater amount of medial compartment lesions in knees with “delayed” ACLR, at 12 months. A study designed to investigate risk factors for OA after ACLR found that partial meniscectomy and a grade three or four chondral lesion at time of surgery were primary risk factors (Cantin et al., 2016). The follow-up was 12 years after ACLR with hamstring or patella tendon graft.

ACL reconstruction

Contemporary methods in ACL reconstructive surgery include a grafting procedure where, in Sweden, the semitendinosus tendon autograft is most commonly used, sometimes necessary to complement with the gracilis tendon. Other autografts used world-wide are patella- and quadriceps tendons. Possibilities of using allografts like patella-, achilles-, hamstring-, tibialis anterior and tibialis posterior tendons are available (Lamblin, Waterman, & Lubowitz, 2013; Landes, Nyland, Elmlinger, Tillett, & Caborn, 2010). Tunnels are drilled in specific angles through the femur and tibia, with reference to the anatomic footprints at the origin and insertions of the ACL. The graft is fit and fixated by, for example, bio-degradable screws for the healing process of tendon into bone. Cortical buttons and transfixational pins are other fixation devices. Patella tendon harvesting consists of also harvesting a bone block from the patella and the tibial tuberosity, for facilitated fixation and healing process. Quadriceps tendon grafts also provide the possibility to include a bony block from the patella.

Double-bundle ACL surgery is an established method, where the aim is to reconstruct the individual bundles of the ACL for improved rotational stability. A Cochrane review of randomized studies found very limited scientific evidence for that the method restores rotatory laxity better than the traditional single bundle surgery (Tiamklang, Sumanont, Foocharoen, & Laopaiboon, 2012). A new Swedish randomized study agrees with this (Karikis, Desai, Sernert, Rostgard-Christensen, & Kartus, 2016). The method requires two tunnels instead of one to be drilled into the femur and tibia respectively, but there are also “hybrid” methods where the numbers of tunnels vary.

Laxity versus functional instability

Antero-posterior joint passive laxity measurements alone, with instrumented (KT1000/ 2000, Rolimeter) or manual (Lachman) testing, do not reflect functional outcome by hopping after ACL injury (Eastlack, Axe, & Snyder-Mackler, 1999; Hurd, Axe, & Snyder-Mackler, 2008; Pollet, Barrat, Meirhaeghe, Vaes, & Handelberg, 2005) or ACLR (Pollet et al., 2005; Sekiya, Muneta, Ogiuchi, Yagishita, & Yamamoto, 1998; Sernert et al., 1999) or functional scores after ACL injury (Eastlack et al., 1999; Pollet et al., 2005; Snyder-Mackler, Fitzgerald, Bartolozzi, & Ciccotti, 1997) or ACLR (Pollet et al., 2005; Risberg, Holm, Tjomsland, Ljunggren, & Ekeland, 1999; Sernert et al., 1999). However, the Pivot shift test is more specific than the Lachman test, and may be a better indicator of whom may suffer from functional instability (Kocher, Steadman, Briggs, Sterett, & Hawkins, 2004). The authors found that a positive Pivot shift test correlated to worse subjective functional scores and subjective sports participation variables after ACLR. A positive Pivot shift test, compared to the Lachman test, was also associated with significantly worse Tegner activity level, Lysholm scores and functional one-leg hop test two years after ACLR, but not at follow-up five to nine years after ACLR (Jonsson, Riklund-Ahlström, & Lind, 2004).

Dynamic, or functional, instability can be evaluated with a battery of objective functional and strength tests and subjective functional knee scores, which may be helpful in determining who can potentially cope with the injury without surgery (Eitzen, Moksnes, Snyder-Mackler, Engebretsen, & Risberg, 2010; Fitzgerald, Axe, & Snyder-Mackler, 2000; Hurd et al., 2008; Kaplan, 2011), and naturally also to assess ACLR outcome (Barber-Westin & Noyes, 2011; Renstrom et al., 2008; Thomeé et al., 2011). Copers are defined as those who have returned to pre-injury athletic activity for at least one year (Snyder-Mackler et al., 1997) without experiencing give way. A Delaware research group developed a screening examination (Fitzgerald et al., 2000) to classify ACL-injured as potential copers or non-copers early after injury to better advise patients for return to pre-injury activity, and to advise patient activity while on waiting lists for surgery (Hurd et al., 2008). The screening defines potential copers, who are more likely to possess dynamic stability and thus have potential capability of returning to a pivoting sport, as those who have had ≤ 1 give way since injury, have rehabilitated quadriceps strength and hop indices to over 80%, and score over 80 and 60%, respectively, on two particular subjective knee function scores. Non-copers are ACL injured who do not achieve these cut-off points after an initial rehabilitation period, and usually ask for ACLR. Other studies have however shown that non-copers with time can become copers (Moksnes, Snyder-Mackler, & Risberg, 2008) and that additional rehabilitation and functional testing may be necessary in order to advise better between those who need ACLR and those who don't (Eitzen et al., 2010). Ongoing research is attempting to specify parameters that can predict when ACL injured are potential copers and do not need surgery, but the wide variety of coping levels and patient activities to examine as well as the lack of advanced randomized prospective studies makes conclusions difficult (Kaplan, 2011). With respect to evidence in the literature it seems warranted, which Kaplan (2011) points out, that

surgeons inform patients of the chance to good knee function via rehabilitation before ACLR is planned and undertaken.

1.2 ACL INJURY AND SURGERY – SPECIFIC BACKGROUND OF THESIS

Gait parameters and muscle activation after ACL injury and surgery

Physiologically, after rupture of the ligament, hemarthrosis causes pain and restricts range of motion, apart from affecting the intraarticular physiology and biochemistry. Joint swelling may also cause reflex inhibition for voluntary quadriceps contraction and strength gain (Palmieri-Smith, Thomas, & Wojtys, 2008). This reflex inhibition is introduced in more detail in the below section of **Muscular, strength and function aspects**.

Quadriceps is an important muscle for controlling weight-bearing onto an extended or semi-extended leg. When muscular knee control fails or becomes inadequate, basic activities like walking and ascending/ descending steps become asymmetric. Mechanically, due to ligament instability, a “shifting” or “give way” sensation may also be subjectively experienced in the knee upon walking or during directional changes.

Sagittal joint angles and moments

Acutely injured subjects and non-copers seem to have similar gait abnormalities with shallower peak knee flexion angles in stance. This creates “stiffening” of the knee or a “non-absorbing” movement pattern in response to ground reaction forces put on the knee. The forces put on the knee joint from body weight in stance provide a decreased knee flexion moment (to be countered by quadriceps postural or eccentric activity) while walking (Chmielewski, Rudolph, Fitzgerald, Axe, & Snyder-Mackler, 2001; Hurd & Snyder-Mackler, 2007; Rudolph, Eastlack, Axe, & Snyder-Mackler, 1998), jogging (Rudolph et al., 1998) and performing other functional tasks (Alkjær, Henriksen, & Simonsen, 2011; J. M. Hart, Ko, Konold, Pietrosimone, & Pietrosimone, 2010; Paterno et al., 2010; Rudolph, Axe, & Snyder-Mackler, 2000). Chronic ACLD patients, as they may be referred to in studies where patient populations are not defined as copers or non-copers, are reported to display abnormalities in their gait pattern several years after the injury (Andriacchi & Dyrby, 2005; Ferber, Osternig, Woollacott, Wasielewski, & Lee, 2002; Torry et al., 2004; Wexler, Hurwitz, Bush-Joseph, Andriacchi, & Bach, 1998). Copers, as specified by criteria as above, walk with movement patterns more like healthy subjects (Rudolph et al., 2000; Rudolph et al., 1998).

The muscles around the joints are viable in maintaining symmetric basic function. Knee joint loading occurs as response to the ground reaction forces in stance phase. In a systematic review by Hart et al. (2010) the authors conclude that ACL injury causes abnormal gait biomechanics, with large differences of sagittal joint moments (the knee flexion moment is lower), in both ACLD and ACLR subjects compared to control subjects. The difference, according to the author, was more obvious for ACLD subjects compared with ACLR subjects, and was also larger when compared to healthy controls. The findings for lower gait knee flexion moments after ACLR were confirmed in the recent systematic review and meta-

analysis from the same authors (H. F. Hart et al., 2016). In the review, studies with opposite results, early (<6 months) postoperative findings of greater knee flexion angle and higher knee flexion moments, are discussed. The authors speculate, that this may explain the gait adaptation needed for the immediate postoperative swelling, pain and inhibited muscle activity. They also reflect on the possibility of this gait pattern being an instigator for future patellofemoral OA. Differences in sagittal joint moments are yet larger (with the knee flexion moment being lower) for more demanding activities like jogging (J. M. Hart et al., 2010). The decreased knee flexion moments after ACLR may take as long as 5 years to restore to fully normal, as concluded by Gokeler et al. in a systematic review (2013), confirmed in a systematic review and meta-analysis by Kaur et al. (2016).

In addition to lower knee flexion moments, increased hip extensor moments have been found and described as compensatory in gait for both ACLD (Hurd & Snyder-Mackler, 2007; Roewer, Di Stasi, & Snyder-Mackler, 2011; Rudolph, Axe, Buchanan, Scholz, & Snyder-Mackler, 2001) and ACLR (Hall, Stevermer, & Gillette, 2012; Roewer et al., 2011) subjects. In the study by Roewer, the compensatory gait patterns for the hip resolved two years after ACLR.

Transverse and frontal plane asymmetries

Rotational offsets have also been found in ACLD and ACLR knees during gait. ACLD subjects, both awaiting surgery (Andriacchi & Dyrby, 2005; Georgoulis, Papadonikolakis, Papageorgiou, Mitsou, & Stergiou, 2003) and long-time injured (Andriacchi & Dyrby, 2005) walk with an internal rotation angle offset found particularly at the end of swing phase/beginning of stance, but maintained throughout the stride. Andriacchi et al. (2006; 2005; 2004) has in a series of papers pointed out that this rotational offset can shift loads in the knee joint. Their research shows that putting load on other areas of the knee joint cartilage, which aren't as physiologically prepared for this load, may cause abnormal cartilage thinning (Chaudhari, Briant, Bevill, Koo, & Andriacchi, 2008). As mentioned above, ACLD subjects who are classified as copers do not show sagittal and frontal plane biomechanic abnormalities during gait. However, the rotational abnormalities may continue to be persistent for ACLD subjects in general (Chaudhari et al., 2008).

ACLR subjects seem to restore excessive rotational abnormalities in walking after ST/G graft (Georgoulis et al., 2003; Webster & Feller, 2011) as well as PT graft (Webster & Feller, 2011). However, there is some debate that more advanced activity demand, such as a 90 degree turn during gait, does not restore tibial rotation after ACLR with ST/G graft (Georgoulis, Ristanis, Chouliaras, Moraiti, & Stergiou, 2007) or PT graft (Ristanis et al., 2006). This was however refuted by Webster et al. (Webster, Palazzolo, McClelland, & Feller, 2012) who found no rotational differences after ACLR with ST/G graft. The authors used the same gait analysis method again (Barenius, Webster, McClelland, & Feller, 2013) and published similar data, where they also concluded that there were no differences in rotation between ACLR subjects with a semitendinosus only- and an ST/G graft. Webster and co-workers (Webster et al., 2012) have suggested that the difference in study results

regarding rotation in these similar gait-and-pivot trials from different research laboratories most likely is attributed to femoral tunnel placement for the respective surgical methods. The authors discuss that a more horizontally placed femoral tunnel, such as in the more anatomical approach with a 9.30 to 10 o'clock position, with the knee in 70 degrees of flexion, will restrain tibiofemoral rotation better than the technique used in the study by Georgoulis et al. (femoral tunnel positioned at 11 o'clock, in 120 degrees of flexion).

Adduction moments of the knee are sparsely mentioned in ACLD and ACLR gait analysis research. One study that assessed adduction moment after ACLR showed that ACLR subjects with a mean of five years since surgery also continue to walk with a 21% greater adduction moment than controls, which is a pattern associated with diagnosed medial OA (Butler, Minick, Ferber, & Underwood, 2009).

The responsive forces of the muscles compressing the joint in loading situations are so far impossible to measure and account for accurately, although mathematic modeling of muscular forces is used to investigate forces put in various joint locations. The authors of a series of animal studies on the subject conclude that muscular adaptations to ACL injury are responsible for abnormal forces onto the knee joint, which bring about OA in the animals (Herzog, Longino, & Clark, 2003).

The influence of quadriceps strength and neuromuscular control on gait

Quadriceps weakness, with side difference of 80% or lower, was found to be associated with decreased knee flexion moments in gait (Lewek, Rudolph, Axe, & Snyder-Mackler, 2002) for both ACLD and ACLR patients with ST/G or allografts. Roewer et al. (2011) in addition found that ACLR subjects had restored bilateral quadriceps strength six months after ACLR with either a ST/G graft or an allograft, but they had not regained symmetric gait patterns regarding knee flexion angles and moments (lower in the involved knee) at peak knee flexion of stance. However, at the two-year follow-up gait patterns had finally become symmetric. Gokeler et al. (2003) found equal isokinetic quadriceps strength in ACLR subjects with PT grafts six months after surgery, but lower knee flexion moments persisted in gait. The lower flexion moments were associated to extension deficits, compared to controls. Webster et al. (2005) also found lower knee flexion moments in midstance of gait particularly for ACLR subject with PT grafts nine months after compared to controls, but isokinetic quadriceps strength did not differ (Webster et al., 2005). Thus, quadriceps strength regain, measured isometrically (Blackburn, Pietrosimone, Harkey, Luc, & Pamukoff, 2016) or isokinetically, may not be enough for neuromuscular- and motor programming in activities like gait after ACLR.

Preoperative rehabilitation with perturbation exercises (which challenges knee control and dynamic balance) instead of strength training alone was found to reduce the preoperative non-coper "stiffening" in gait in subjects tested six months after subsequent ACLR with ST/G graft or allograft (E. Hartigan, Axe, & Snyder-Mackler, 2009). Both the perturbation and the strength training only group had at six months after surgery regained bilateral quadriceps

strength, indicating that specific neuromuscular rehabilitative challenge such as perturbation training may be needed to resolve limb symmetry for walking. The same authors found that preoperative results of equal quadriceps strength, symmetric knee flexion moments in stance of gait (countered by eccentric quadriceps muscular activity) as well as a younger age predicted return to sports six months after ACLR (E. H. Hartigan, Zeni, Di Stasi, Axe, & Snyder-Mackler, 2012). However, the same method of training applied postoperatively was not effective for male athletes in regaining gait symmetry for knee and hip excursion in mid-stance, one to two years after ACLR (Capin, Zarzycki, Arundale, Cummer, & Snyder-Mackler, 2017).

EMG parameters

Muscular activity patterns and muscular contraction intensities (relative to a maximum voluntary isometric contraction) are measured by electromyography (EMG) to clarify biomechanical findings further. Studies of gait analysis with EMG in the 80's and 90's (Devita et al., 1997) have reported that muscle activity patterns in gait for both ACLD and ACLR subjects show decreased quadriceps and increased hamstring activity in preparation for and during stance. The increased hamstring activity, and lowered quadriceps activity, was initially thought to be an adaptation for ACL stability particularly in acute and non-coping ACLD patients. The involuntary decreased use of the quadriceps in stance was thought to decrease excessive anterior tibial translation (Berchuck, Andriacchi, Bach, & Reider, 1990). The term “quadriceps avoidance” was coined when the authors found that, for chronic ACLD subjects, reduced stance knee extension angles (as mentioned above is a common finding in ACLD and ACLR subjects before thorough rehabilitation) and extensor moments were related. The study did however not include EMG. Some authors who have used EMG have since refuted that there is lower quadriceps activity (Ferber et al., 2002; Knoll, Kiss, & Kocsis, 2004; Roberts, Rash, Honaker, Wachowiak, & Shaw, 1999) but they did find hamstring activity of greater magnitude or duration.

More recent studies have been able to delineate muscular adaptations further: In the dynamically unstable knee (as for acutely or sub-acutely injured and for non-coping ACLD subjects), quadriceps and hamstrings timing adaptations cause co-contractions during gait (Hurd & Snyder-Mackler, 2007; Rudolph et al., 2001; Rudolph et al., 1998; Torry et al., 2004). Increased magnitude hamstring activity is also thought to cause the “stiffness” or non-absorbing mechanics in the knee, seen by less knee flexion angles (and lower external knee flexion moments, as mentioned above) in stance of gait. Muscle forces are thought to contribute as additional compressive joint forces at weight acceptance (Hurd & Snyder-Mackler, 2007). ACLD subjects who are classified as copers or potential copers on the other hand have more normal external knee flexion moments (which are counteracted by quadricep eccentric forces), knee flexion angles and quadricep-hamstring activity patterns, similar to healthy subjects in walking (Rudolph et al., 2001; Torry et al., 2004) and jogging (Rudolph et al., 2001).

Muscular, strength and function aspects after ACL injury and surgery

Hypotrophy

Unfortunately not all patients regain proper bilateral strength and muscle mass after an injury of larger magnitude or long convalescence. The adaptive muscular patterns during functional performance may then put excessive strain on the joint. Quadriceps hypotrophy is a fact after injury and surgery. Bilateral imaging with CT and MRI has shown up to 10% deficits of quadriceps cross-sectional area (CSA) for ACLD subjects after the rehabilitative period (Konishi et al., 2011; Lorentzon, Elmqvist, Sjöström, Fagerlund, & Fuglmeyer, 1989; Williams, Buchanan, Barrance, Axe, & Snyder-Mackler, 2005). After ACLR, authors have observed the same quadriceps hypotrophy for subjects with PT and other grafts (Arangio, Chen, Kalady, & Reed, 1997; Risberg, Holm, Steen, Eriksson, & Ekeland, 1999; Thomas, Wojtys, Brandon, & Palmieri-Smith, 2016), and for ST/G grafts, (Eriksson et al., 2001; Konishi, Ikeda, et al., 2007; Williams, Snyder-Mackler, Barrance, Axe, & Buchanan, 2004) sometimes years after surgery. Other than the obvious relationships between quadriceps hypotrophy and knee extensor strength, tested by isokinetics or maximum voluntary isometric contraction (MVIC), there's evidence that hypotrophy alone doesn't account for all of the strength loss in ACLD subjects (Konishi et al., 2011; Lorentzon et al., 1989; Williams et al., 2005) and ACLR subjects (Konishi, Ikeda, et al., 2007; Konishi, Oda, Tsukazaki, Kinugasa, & Fukubayashi, 2012). Muscle strength decrease may thus also include components of disrupted neuromuscular activation, introduced in the section *Neuromuscular associations to muscle morphometry* below.

Arthrogenic muscular inhibition (AMI)

Patients with mild as well as extensive knee injury or osteoarthritis, or as a postoperative condition, may suffer from arthrogenic muscular inhibition (AMI). AMI refers to an extended period of quadriceps inhibition, thought to affect proper short- and long term muscle activation and strength gain. Joint effusion, inflammation, pain, joint laxity, and structural damage of capsule or ligaments can cause AMI. It is explained as a reflex inhibition: When altered afferent stimuli from injury or surgery are transmitted to the central nervous system, it results in decreased spinal reflex excitability and muscle activation. Diverse mechanisms for AMI are explained and reviewed by Rice et al. (2010; 2014) and Ingersoll et al. (2008). It is important for clinicians to recognize and understand some of the physiologic and neurologic framework of AMI, since effects can be long lasting and impair muscular control and strength increase. The perhaps most obvious reason for quadriceps inhibition is presence of effusion. Neurophysiological research has found clear evidence, in knees with effusion, for decreased function in afferent input which makes it more difficult for alpha motor neurons to work and contract muscles properly: Surprisingly small amounts of fluid injected into healthy knee joints seem to increase intra-articular pressure on joint surfaces and produce quadriceps inhibition (Rice & McNair, 2010; Wood, Ferrell, & Baxendale, 1988). In an ACL-injured population decreased quadriceps activation response to effusion was found but not in all patients (Lynch, Logerstedt, Axe, & Snyder-Mackler, 2012).

Some of the mechanisms that are thought to cause AMI are neuromuscular. Konishi and colleagues have studied the relationship of quadriceps muscle volume and isokinetic knee extensor strength both for ACLD and ACLR subjects. From the results they infer that it isn't solely hypotrophy which is responsible for decreased quadriceps isokinetic strength. Their extensive research was initially on the gamma loop/ reflex arc, with stimuli on the patella tendon (Konishi, Aihara, Sakai, Ogawa, & Fukubayashi, 2007; Konishi, Fukubayashi, & Takeshita, 2002a, 2002b; Konishi, Konishi, & Fukubayashi, 2003; Konishi, Suzuki, Hirose, & Fukubayashi, 2003). The focus is on the possible neurological mechanisms that the gamma motor neurons have become dysfunctional due to the ruptured ACL. Their theory is that after injury, recruitment of high-threshold motor fibers may be impaired by loss of afferent feedback because of the rupture of the ACL. Difficulty recruiting high-threshold motor units may make full strength gain difficult long time after injury and surgery, and possibly not resolve for the ACLD leg. Fourteen months (range 4-91) after injury, ACLD subjects had lower muscle volumes and lower peak torques in their injured leg than in the healthy leg compared to controls, and bilaterally lower muscular peak torque per unit muscle volume than controls (Konishi et al., 2011). In ACLR subjects with quadruple ST graft, high-threshold motor unit recruitment of the quadriceps was restored at 18 months after ACLR (Konishi, Oda, et al., 2012) but not at 12 months after ACLR (Konishi, Ikeda, et al., 2007). Bilateral neuromuscular deficits are also reported (Harkey et al., 2016; Konishi, Aihara, et al., 2007). Previous authors have furnished results which may be explained by the research of Konishi et al. (Lorentzon et al., 1989; Urbach & Awiszus, 2002; Urbach, Nebelung, Weiler, & Awiszus, 1999), where the hypotrophy could not explain all of the strength loss.

Hamstring muscles do not show neurologic dysfunction in terms of muscular recruitment after ACL injury (Konishi, Kinugasa, Oda, Tsukazaki, & Fukubayashi, 2012). Hamstring muscle volume with MRI also showed no differences between ACLD leg, healthy leg and controls at least 4 months (4-91) after ACL injury, and neither did the muscle peak torques per muscle volume. After ACLR, the same method showed differences in hamstring muscle recruitment per unit volume which the authors however did not consider as neurological dysfunction due to the ACLR. The reason for this was that both the reconstructed and the healthy leg 12 months postoperatively were significantly different compared to control, and also that the results could be biased by the effect from the harvest of the tendon (Konishi & Fukubayashi, 2010). Strength had recovered to 90% between the reconstructed and healthy leg, tested isokinetically in a seated position.

Strength and function

Quadriceps strength deficits have been recorded as high as 20% and more, sometimes several years after ACLR (Palmieri-Smith et al., 2008). Recent reviews agree to this: Lepley et al. (2015) reports 14% quadriceps deficit 12 months after ACLR, with some lower percentages for ST and ST/G grafts versus PT grafts. Authors of a Cochrane systematic review (Mohtadi,

Chan, Dainty, & Whelan, 2011) report that quadriceps strength in subjects reconstructed with a PT graft shows a trend towards decreased strength outcome results, at a minimum of two years after surgery, as compared to subjects with a hamstring graft. The review from 2008 by Palmieri-Smith et al. Palmieri-Smith et al. (2008) states that quadriceps strength deficits in many of the reviewed studies were alarmingly large at the time where many athletes were allowed to resume competitive sports. Conventionally, at the time, this was approximately from 6 months postoperatively and on. Strength recovery after ACLR has been found to correlate to preoperative quadriceps strength (Eitzen, Holm, & Risberg, 2009).

Quadriceps strength has been found to correlate to subjective functional scores (de Jong, van Caspel, van Haef, & Saris, 2007; Goradia, Grana, & Pearson, 2006; Keays, Bullock-Saxton, Newcombe, & Keays, 2003; Sernert et al., 1999) and to predict IKDC 2000 and other function scores (Eitzen et al., 2009; D. S. Logerstedt et al., 2010). Quadriceps strength has been found to correlate to frequently used functional hop tests in ACLD and ACLR subjects for ST/G grafts (Keays et al., 2003) and PT grafts (de Jong et al., 2007; Wilk, Romaniello, Soscia, Arrigo, & Andrews, 1994) and in a mixed cohort of PT and hamstring grafts (Schmitt, Paterno, & Hewett, 2012). Quadriceps strength in healthy individuals correlates to hop tests (Hamilton, Shultz, Schmitz, & Perrin, 2008; Pincivero, Lephart, & Karunakara, 1997) but not when accounting for weight, height and age (Ostenberg, Roos, Ekdahl, & Roos, 1998). Further, it has been advocated that the single leg hop should be rehabilitated to at least 90% when comparing the reconstructed to the healthy leg (Augustsson, Thomeé, & Karlsson, 2004) before safe activity return may be allowed.

Hamstring strength deficits are obvious, due to the process of the regenerating tendons, after reconstruction surgery with the use of an ST/G graft. Studies have reported deficits in deep angle of knee flexion, specifically when measured in prone position with isokinetic strength tests, after two (Choi JY 2011, Kim 2011, Elmlinger 2006) and six years postoperatively (Elmlinger, Nyland, & Tillett, 2006; Kim et al., 2011; Åhlén, Lidén, Bovaller, Sernert, & Kartus, 2012) .

Rehabilitation after ACL injury and surgery

Initial rehabilitation after ACL rupture concerns acute phase monitoring of the swelling, restoring joint movement and restoring symmetric basic knee-function such as for example gait, balancing and stair-stepping. Continued rehabilitation explores and challenges functional and muscular limits and the goals are to be able to return to normal activity. Neuromuscular control, balancing and progressive lower extremity, hip and core strength exercises begin at elementary levels and advance as far as tolerated to more dynamic and sports-specific activities. Rehabilitation after ACL reconstructive surgery has similar stepping stones with some time-restrictions due to initial graft and fixation protection and concern to the regenerating tendons. Rehabilitation protocols should include neuromuscular training as well as strength exercises and sport specific training for optimal results (D. S. Logerstedt et al., 2010; Myer, Paterno, Ford, & Hewett, 2008; Risberg, Holm, Myklebust, & Engebretsen, 2007; Shelbourne & Klotz, 2006; van Grinsven, van Cingel, Holla, & van Loon, 2010).

Immediate postoperative bracing for protective reasons does not, according to systematic reviews (Andersson, Samuelsson, & Karlsson, 2009; Wright & Fetzner, 2007), make a difference in outcome after ACLR. It is conclusive in literature that variables of range of motion, laxity, strength, functional tests and functional scores aren't different for brace- and non-brace groups. However, almost conclusively all studies referred to on the topic are performed on ACLR subjects with a PT graft (Brandsson, Faxén, Kartus, Eriksson, & Karlsson, 2001; Harilainen & Sandelin, 2006; Möller, Forssblad, Hansson, Wange, & Weidenhielm, 2001; Risberg, Holm, Steen, et al., 1999). Muscular shortcomings may affect function and stability, and there has been a need for information if absent hamstring tendons would benefit from an immediate postoperative brace on account of muscular- and joint conditions, stability, and function. To the best of our knowledge, only one randomized study on postoperative bracing after ACLR with hamstring graft has been published after the initiation of our research (Ito et al., 2007). The authors found no difference in strength, joint position sense or laxity (follow-up at three, six and twelve months) between those who had a brace for three days or those who had a brace for two weeks after ACLR. Other functional parameters were not tested.

1.3 EVALUATIVE METHODS FOR ACL INJURY AND SURGERY

Gait analysis (i.e. motion analysis, movement analysis), electromyography (EMG) and computed tomography (CT) are some evaluation measures for the research in this thesis and warrant separate introduction:

Gait analysis

Gait- or motion analysis is a non-invasive method for investigating specifics of joint dynamics; segmental motion, joint angles and joint moments in various functional positions. The term kinematics refers to the description of motion. Kinetics refers to forces, moments, masses and accelerations. Combined kinematic and kinetic data allows quantifying motion analysis. Three-dimensional motion analysis requires a setup of a subject with skin-markers placed in anatomically known positions of specific reference- and bony landmarks. Several cameras (at least two are required) which capture the movement of the markers from all directions around the marker set-up usually surround the laboratory space. After capturing the movement of the markers, they can be traced in software programs, and pre-programmed mathematical computation can provide temporal and spatial data from three planes for the joint and/ or body segments, in reference to a pre-calibrated laboratory space. The three-dimensional kinematic information of intricate joint angles, body-segment motion and speed of motion is complemented with kinetic information of reactive forces from force plates, measuring ground reaction forces. Force plates measure vertical, antero-posterior and lateral forces at high precision, as well as taking into account the rate of the force. The action on the joint during the joint motion; the inverse dynamics of joints, then allow joint moments and muscular power to be calculated. Interpretation of such data is still not without challenge, as the diverse scenarios of co-activating muscle forces around the joint, or nearby joints, may be included on theoretical basis in formulae, but not measured and applied directly. The

calculations are highly dependent on correct marker placement so body segments can be properly defined in three dimensions, and joint centers can be located mathematically. The extensive details of human gait can be studied in recognized works from Winter (2009) and Rose and Gamble (2006).

The accuracy of the cameras tracking the markers is as high as 1 mm (Maletsky, Sun, & Morton, 2007; States & Pappas, 2006; Winter, 2009) but this non-invasive biomechanic evaluation has other limitations: The motion between the markers and the skin in human motion, so called soft tissue artifacts, have been reported to be up to 10 mm (Gao & Zheng, 2008; Garling et al., 2007; Manal, McClay Davis, Galinat, & Stanhope, 2003) and 15 mm (Peters, Galna, Sangeux, Morris, & Baker, 2010) on the lower leg, more on the thigh, and there's also rotational displacement (Akbarshahi et al., 2010). Sagittal plane angles are not very affected by this due to long segment arms but other planes, joint moments and powers may be more influenced (Gao & Zheng, 2008; Tashman & Araki, 2013). However, the alternatives of non-invasive motion analysis are recent dynamic radiographic MRI techniques which are more limiting in sampling frequency (suitable for static or very slow movement, in very limited space) and three-dimensional fluoroscopy (suitable for movement tasks in a small space) (Gao & Zheng, 2008; Tashman & Araki, 2013).

Electromyography

Electromyography (EMG) measures the motor unit action potential, i.e. the electrical activity of the contracting muscle. Skin preparation and rigid adhesion of the electrode to the skin is required to optimally transmit signals through the electrode. The action potential picked up by the electrode is the sum of the action potentials of many nearby motor units of superficial muscles, approximately from within 25 mm of the skin surface (Whittle, 2002). Thus there is a discrepancy as to interpreting data from isolated muscles, and also as to comparing between subjects. For investigation of deep muscles, fine-wire electrodes are used but data from such electrodes is not as reproducible due to the more local and much smaller zone of electric activity pick-up (Winter, 2009). Movement artifacts and speed of muscle contraction are limiting factors, which makes it difficult to quantify EMG data for interpretation. Researchers use a relative comparison of the EMG signal, for example to the signal of the isometric maximum (or submaximal) voluntary muscle contraction. This makes it possible to discuss the rates of the magnitude of the contraction. Ratios between antagonists and synergists can be explored in a similar relative way. All analyses of muscle activity require defining the base level activation when the muscle is "silent", which is usually in quiet standing, as compared to the onset of activity. The electrodes are placed at recommended locations in order to achieve optimal reproducibility. The EMG signals are valuable indicators when evaluating timing of the muscle actions or muscular activity patterns such as on- and off-set (Shumway-Cook, 2001). The recognized muscular patterns of gait have been examined in detail by for example Basmajian (1985). Whittle (2002) has reported on similar but not identical gait muscle activity data. Many of the muscles are active for less than 0.2 seconds in and around

stance, where stance itself may be around 0.6 seconds. As mentioned, EMG registers the electrical activity of the muscle and cannot distinguish type of contraction.

Computed Tomography

Imaging techniques constantly improve and open for new clinical and research possibilities. For the research presented in this thesis, computed tomography (CT) was the selected method due to the advantages of CSA analysis as well as the ease of joint effusion measurements at the initiation time of the studies. CT is successfully used in studies focusing on muscular CSA, as a measure of hypo- and hypertrophy of musculature compared to a baseline or to the contralateral leg (Berg, Dudley, Häggmark, Ohlsén, & Tesch, 1991; Berg, Eiken, Miklavcic, & Mekjavic, 2007; Hahn & Won, 2016; Rasch, Byström, Dalén, Martinez-Carranza, & Berg, 2009). This is also an established method to study muscle density in healthy persons and patients with varied diagnoses (Goodpaster, Thaete, & Kelley, 2000; Hahn & Won, 2016; Kelley, Slasky, & Janosky, 1991; Manini et al., 2007; Rasch, Bystrom, Dalen, & Berg, 2007).

Fatty infiltration may appear in muscle tissue on CT or MR imaging after inactivity in healthy subjects as well as after injury and surgery. The radiodensity, or density, of muscle tissue may be measured by CT in Hounsfield units (HU), which has a definition of being 0 for water and -1000 for air. Most soft tissue has values above zero while adipose tissue generally has values below zero. The ranges for defining skeletal muscle tissue versus adipose tissue and bone have varied in the literature (Strandberg, Wretling, Wredmark, & Shalabi, 2010). For skeletal muscle, Goodpaster et al. (2001; 2000; 2000) and Kelley (1991) have used ranges of roughly 0-30 HU for low density muscle tissue and up to 100 HU as normal density muscle tissue. A decrease in muscular CSA and an increase in fatty tissue decreases the radiodensity (density) of a muscle and may be related to change in muscle function (Berg et al., 1991; Manini et al., 2007; Rasch et al., 2009). The ranges of what is considered high and low density muscle may be debatable, but Kelley (1991) established that the proportion of low density muscle tissue is far greater in obese subjects. Associations between CSA, strength, function and muscle density are so far fairly un-explored in ACL populations.

2 AIMS

The overall aim was to examine basic gait function and muscular activity patterns for possible deviations, and to investigate joint effusion, decreased muscular cross-sectional area and muscle quality as they are obstacles in the rehabilitative course.

Specific study aims were:

Study I

To analyze and describe three-dimensional gait and EMG activity patterns in long-time ACL-injured subjects (ACL copers) and in healthy control subjects.

Study II

To analyze and describe muscular morphometric CSA in various muscles of the thigh after ACL injury but before ACL reconstruction. Another aim was to investigate possible influence on the CSA from prior meniscus injury, side of injury, limb dominance or physical activity level, and to evaluate if there were sex differences.

Study III

To analyze and describe muscular morphometric changes in muscular CSA and density in various muscles of the thigh, prospectively, before and one year after ACLR. A second aim was to investigate if changes in muscular CSA and density would affect clinical one-year outcome variables.

Study IV

To analyze and describe the course of joint effusion in ACL injured and subsequently reconstructed knees, before as well as three and twelve months after ACLR. The aim was also to investigate whether presence of knee joint effusion was affected by postoperative brace regime. Another aim was to identify predictors associated with presence of three-month effusion, and to assess if this effusion was associated to one-year outcome.

Study III and IV

To analyze if a postoperative brace affects general outcome one year after ACL surgery with ST/G graft.

3 METHODS

Two different experimental study-settings build the foundation of this thesis. One setting (clinical and laboratory/ biomechanical) investigates the function of gait and muscular patterns of gait activity in ACL injured copers. The other setting (clinical and laboratory/ radiological) investigates decreased muscular cross-sectional area and muscle quality as well as possible obstacles of joint effusion, in the rehabilitative course before and after ACL reconstruction.

3.1 STUDY DESIGN AND ETHICAL APPROVAL

The research for this thesis is conducted in two separate clinical trials. Measures include quantitative variables from three-dimensional movement analysis, electromyography (EMG) and CT data, as well as clinical tests and subjective questionnaires. See **Table 1** for study designs. Upon recruitment and inclusion, all subjects received written and verbal information about participation and test procedures, and signed an informed consent. Participation was voluntary and the subjects were informed that they at any time could withdraw without any given reason. The studies were approved by the local Ethics Committee, registration number 162/02.

3.2 SUBJECTS

Two different patient-type groups and one group of healthy controls have been examined in the scope of the thesis. As seen in Table 1, ACL copers, or chronic ACLD subjects, and a group of healthy controls were examined in study I. There were 62% men, which is fairly comparable to the regular incident rate in Sweden of about 60% (Nordenvall et al., 2012). For study II, ACL injured subjects were examined prior to ACLR, and for studies III-IV, ACLR subjects were examined pre- and postoperatively. This group was comparable to an ACLR sample of the Swedish population on account of age and male – female proportion, according to the Swedish National ACL registry (Nordenvall et al., 2012).

Table 1. Study design, subjects, study elements and measures.

Study	Type	Subjects	Elements	Measures
I.	Cross-sectional	16 ACL-injured persons (6 women, 10 men) 15 healthy controls (9 women, 6 men)	Clinical and laboratory trial Questionnaires	Three-dimensional movement analysis EMG Activity scale Subjective knee score Clinical tests
II.	Cross-sectional	62 ACL-injured persons before ACLR (22 women, 40 men)	Clinical and laboratory trial Questionnaire	CT Activity scale
III.	Prospective	37 ACL-injured persons before and after ACLR. (14 women, 23 men from study II)	Clinical and laboratory trial Questionnaires	CT Activity scale Subjective knee scores Clinical tests Functional tests
IV.	Prospective randomized controlled	60 persons before and after ACLR. (22 women, 38 men; 58 persons from study II)	Clinical and laboratory trial Questionnaires	CT Activity scale Subjective knee scores Clinical tests Functional tests

Study I

All ACLD subjects (6 women, 10 men, mean age 39 years) had previously been seen at the Karolinska University Hospital Orthopedic Clinic and had ACL-injuries, conservatively treated, for at least one year. The subjects were satisfied with their knee and their activity level, and had not asked for nor been recommended ACL reconstructive surgery. They were recruited by diagnostic code, contacted in backward chronological order since the last clinic visit, and asked about volunteering for the study. A group of healthy control subjects (9 women, 6 men, mean age 25) were recruited for comparison of data. The groups were unmatched.

Study II

ACL-injured subjects (22 women, 40 men, mean age 27 years) planned for ACLR were recruited from the Karolinska University Orthopedic Clinic at Huddinge between 2003 and 2006. Inclusion criteria were a unilateral ACL-injury without associated ligamentous or chondral injury, diagnosed by arthroscopy, clinically or by MRI, and a healthy contralateral leg. Patients with a prior partial meniscus injury were included, as long as the injury was not surgically repaired.

Study III-IV

As in study II, the same type of ACL-injured subjects planned for ACLR formed the different populations for the studies. Study III included 13 women and 24 men; mean age 26 years, and study IV included 22 women and 38 men; mean age 25 years. The age ranges were 16-55, and patients in the upper age range (46-55) were found to equally have lowered their pre-injury activity due to the injury as compared to the younger, and they were later equally satisfied with their surgery outcome. Inclusion criteria were the same as for study II: Unilateral ACL-injury without associated ligamentous or chondral injury, diagnosed by arthroscopy, clinically or by MRI, and a healthy contralateral leg. Patients with a partial meniscus injury or meniscectomy were included, as long as no surgical repair was performed or indicated.

Randomization of subjects for study III-IV

At the preoperative visit the patients were randomized into two groups; wearing or not wearing an immediate postoperative brace for three weeks after surgery. In the order of recruitment, patients were thus drawing numbered, pre-sealed envelopes prepared with randomly drawn group assignments. The envelopes were prepared by computer randomization at the department secretarial office. The brace was an immobilization-type brace (Hypex light, Aircast, Albrecht GmbH, Stephanskirchen, Germany.). The brace-group wore the brace immediately after surgery, locked in extension when standing and walking, for three weeks. For both groups, full weight-bearing with the use of two crutches was allowed.

3.3 SURGICAL PROCEDURE (STUDY III-IV)

ACL reconstruction was performed as out-patient day-surgery with a semitendinosus-gracilis (ST/G) graft. Three experienced surgeons used a standardized single tunnel approach and uniform fixation devices.

3.4 REHABILITATION PROTOCOL (STUDY III-IV)

The patients were not systematically enrolled in a clinic-specific pre-ACL reconstruction rehabilitation program. Postoperatively the patients were allowed full weight-bearing as tolerated, with the use of two crutches. The patients were carefully instructed in the preoperative visit, both verbally and by a written exercise protocol, to exercise four times daily for the first three weeks. The initial exercises were knee flexion/ extension range of motion, quadriceps contractions seated with a straight leg, and hand-supported bilateral heel-raises. The instructions and exercises were reinforced in the first postoperative visits. Beginning the fourth postoperative week, focus was on basic functional symmetries and closed chain exercise. The rehabilitation protocol used in the present study was mainly based on closed kinetic chain/neuromuscular control exercises. Task-specific quality of movement and movement symmetry was expected in order to advance into each next phase, along with respective adequate amount of neuromuscular control, strength, and balance. Exercise bike

was allowed after three weeks, and jogging was allowed after three months (see Appendix in study III and IV). Three experienced physical therapists from the same clinic managed the rehabilitation.

3.5 DATA COLLECTION AND PROCESSING

The test protocol used in studies III - IV is given in Table 3.

Table 3. Test protocol for studies III - IV

Preoperatively	3 months postoperatively	12 months postoperatively
CT 5 and 15 cm above joint-line	CT 5 and 15 cm above joint-line	CT 5 and 15 cm above joint-line
Heel height difference	Heel height difference	Heel height difference
Flexion – extension endpoints	Flexion – extension endpoints	Flexion – extension endpoints
Rolimeter® laxity		Rolimeter® laxity
One leg hop		One leg hop
Lysholm score		Lysholm score
Tegner activity scale		Tegner activity scale
IKDC activity definition		IKDC activity definition
KOOS		KOOS
		Triple hop
		6 m timed one leg hop
		Square hop test

Laboratory measurements

Gait analysis for study I

An 8-camera system (Elite, BTS, Milano, Italy) recorded positions of 13 passive light-reflecting markers, placed on bony landmarks and segments of the lower leg (Figure 1). Marker placement was on the L4 spinous process, the posterior iliac spines, greater trochanters, lateral femoral epicondyles, lateral malleoli, the posterior calcanei and the fifth metatarsal heads. The position of the markers was calibrated into a 2x2 m space surrounding floor-levelled force plates (500 x 500 mm², Kistler, Winterthur, Switzerland). Vertical, antero-posterior and medio-lateral forces as well as the position of the skin markers were recorded at a sampling frequency of 100 Hz. The subject walked, at self-selected speed, on a 10-m runway over the force plates (Figure 2). From the gait trials, five clean foot strikes onto the force plate were collected each foot. For healthy control subjects (study I) data was collected from a total of five foot-strikes from any foot. After data processing (see below) an average of the five foot-strikes were used for statistical analysis.

Figure 1. Calibrated space and forceplates.

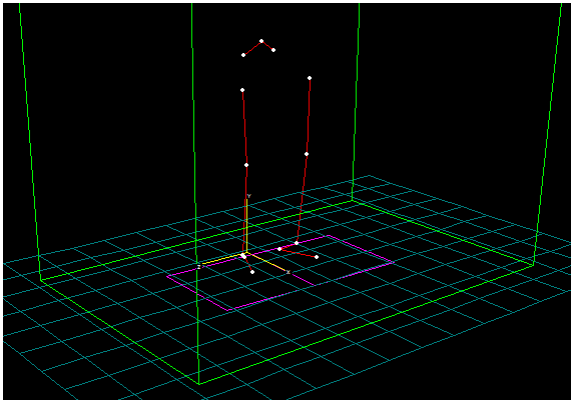
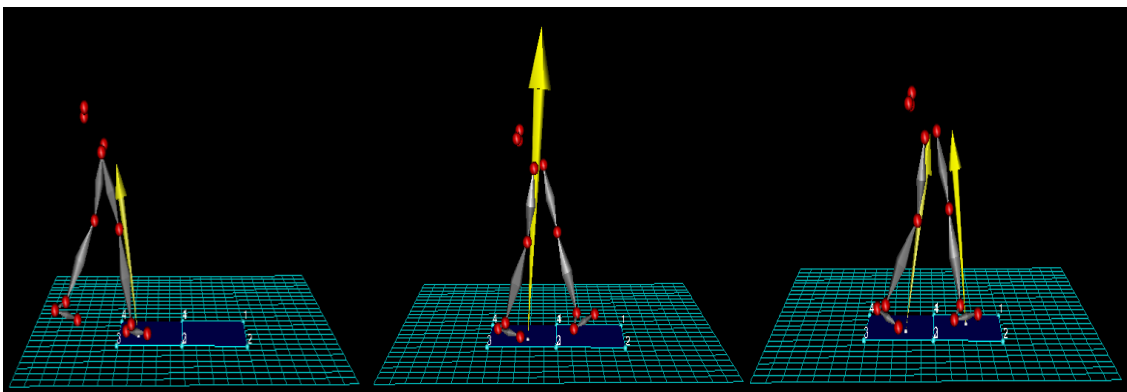


Figure 2. Subject with skin-markers generating ground reaction forces.



Kinematic data for study I

The raw data files were processed, computed and converted to text-files in Biomech 2.0.1., in the Visual 3D software application (BTS, Milano, Italy): Foot- and knee angles in stance and swing were computed from trigonometric formula programs, after the input of the respective selected marker set segments. The angles computed for stance phase were maximum knee flexion and maximum ankle dorsiflexion. The knee flexion angle was also computed at initial contact of stance phase. In swing phase maximum knee flexion was computed.

Spatial and temporal data for study I

Raw data files were processed and converted to text-files in Biomech 2.0.1. Visual 3D software. Stride length, stride time, gait speed and heel lift height in swing was then analyzed in Axograph 4.9 (Axon Instruments, Union City, CA).

Kinetic data for study I

Raw data files were processed to text files in the Biomech 2.0.2 software. The vertical (Fz) and antero-posterior (Fy) force peaks of stance phase were identified in Axograph 4.9 and normalized to % of bodyweight. The time for the force peaks was calculated in % of stance phase time, beginning at initial contact and ending with toe off.

EMG

EMG was recorded simultaneously (Bagnoli 8, Delsys, Boston, USA). The EMG electrodes were bipolar with an inter-electrode distance of 10 mm. The electrodes had a built-in gain amplification of 10, and sampling frequency was 1000 Hz. After conventional skin preparation they were attached with adhesive tape over the bellies of the muscles bilaterally on the vastus medialis portion of the quadriceps, biceps femoris, lateral gastrocnemius and the anterior tibialis, according to guidelines outlined by authors in the SENIAM (Surface Electro-Myography for the Non-Invasive Assessment of Muscles) project (Hermens, 1999).

Raw EMG data for each synchronous trial from the gait analysis was rectified and processed to text files in the Myolab software (BTS, Milano, Italy). Data was then filtered and analyzed in Axograph 4.9 (Axon Instruments, Union City, CA). The muscle on-set and off-set activity pattern in preparation for and during stance was analyzed: A muscle was considered active when activity was at least two standard deviations above baseline with a duration of at least 30 milliseconds, and offset time was regarded as the time when activity decreased to a value lower than two standard deviations above baseline and was kept at this level for more than 30 ms (Hirschfeld, 1997).

Computed tomography

Cross-sectional images by CT were attained from the ACLR patients preoperatively and 3 and 12 months after ACLR. A Philips Tomoscan SR 7000, single-slice helical CT scanner, 100 kV and 75 mAs, (Philips Medical Systems Nederland B.V., Eindhoven, the Netherlands) was used for the majority of the examinations. Slice thickness was 10 mm.

CT for study II and III

Muscular cross-sectional area of the thigh was investigated at 15 cm proximal to the knee joint line for the muscle groups of the quadriceps as a whole, the biceps femoris, the semimembranosus, the sartorius, the semitendinosus and the gracilis. The four separate muscles of the quadriceps group and the two of biceps femoris could not be reliably separated for the analysis. The muscle borders were outlined, and the area (mm²) inside the borders with the attenuation measure of 1-101 HU was measured. This includes both low density and normal density muscle, and excludes fatty tissue within the area. The data was analyzed with NIH ImageJ version 1.42e software packages. These are continuously updated and freely available from the U.S. National Institute of Health (Rasband, 1997-2017). Compared with the contralateral thigh, CSA thus gave an indication of muscularly hypo- and hypertrophy. For study III, the mean attenuation value (mean HU) was also recorded and analyzed as a measure of muscular density. The measurements were recorded by an experienced radiologist. The method has been evaluated with repeated measures and found to have good reliability (Strandberg et al., 2010).

CT for study IV

Presence or absence of joint effusion was investigated at 5 cm proximal to the knee joint line, which besides the joint space also targets the suprapatellar recess area. Two experienced radiologists recorded the presence or absence of joint effusion in the images. The inter-tester reliability (R) was examined by separate measures to be 0.93%.

Clinical measurements

All clinical tests were performed according to a standardized protocol. Three experienced physical therapists performed the measurements for the ACLR population.

Knee laxity

Knee laxity was tested at manual maximum with a Rolimeter® (Aircast, Summit, New Jersey, USA). The knee was kept in 20-30 degrees of knee flexion, with the knee resting on a cylindrical pillow with a 10 cm diameter (Muellner, Bugge, Johansen, Holtan, & Engebretsen, 2001). Three measurements were performed and the median was recorded. Results are given as the difference between the laxity in the injured and the un-injured knee.

Knee range of motion

Passive knee range of motion was measured with a handheld goniometer, patient in the supine position, goniometer arms lined up with the greater trochanter and the lateral malleolus with the center of the goniometer at the lateral epicondyle of the femur (Greene & Heckman, 1994). The heel was resting on a 10-cm cylindrical hard pillow for the extension measure. Full flexion was recorded while some part of the sole of the foot was still in contact with the patient table.

Heel-height difference

Heel-height measurement (Figure 3) was used to document knee extension range of motion (Schlegel, Boublik, Hawkins, & Steadman, 2002). The heel-height measuring tool consists of a vertical measure-stick, scaled in cm, with a level which controls horizontal positioning. Heel-height difference was measured with the subject prone on the treatment-table. The patellae rested on the edge of the table and the lower legs were hanging off the edge. The subject's hips were secured with a strap.

Figure 3. Heel-height measure.



Functional hop tests

The one-leg hop test, the triple hop, the 6 m one leg hop and the square hop tests were measured. The tests are commonly used and proven reliable and all but the square hop test have also been tested for validity for ACLR subjects (Ostenberg et al., 1998; Reid, Birmingham, Stratford, Alcock, & Giffin, 2007). All hop tests were performed with standardized instructions 1 year after surgery, and subjects also performed the one-leg hop preoperatively. The distance hops and the 6 m timed hop were performed three times for each leg, and the best measure for each leg was selected. The square hop test was performed 30 seconds on each leg. The tests for each subject followed the order mentioned, and subjects always started with their un-injured leg:

The one-leg hop measures the distance of the hop, providing landing is controlled. Free arms were allowed as opposed to hands on the back. Three hops were performed with each leg

The triple hop measures the distance of three hops (on the same leg) in a sequence, provided landing is controlled.

The 6 m one leg hop measures the time it takes to hop a 6 m distance, and the time was measured. The subject was placed 1 m behind a set of photo cells (Alge Timing, Sweden) and timing began and ended as the photo cell line was crossed.

The square hop test utilizes a 30 x 35 cm rectangle drawn on the floor. For 30 seconds the performer hops in and out of the rectangle in a clockwise direction. The test result is the number of times that the foot is placed within the borders of a 30 x 35 cm rectangle.

Subjective scores

The Lysholm Knee Score documents patients' symptoms, stability and function of the knee, with a best possible score of 100. It was originally constructed to evaluate outcome of ligamentous knee surgery (Lysholm & Gillquist, 1982), but has since been modified as well as validated for a variety of knee conditions such as meniscal and articular cartilage injuries and patella dislocations (Briggs, Kocher, Rodkey, & Steadman, 2006; Briggs et al., 2009). The score can be self- or, as in or work, assessor administered although originally designed to be physician-administered. Decreased function from any of the categories of limping, use of a walking aid, swelling, stair climbing, squatting, instability, pain or locking lowers the score. From 65 points the result is considered fair, from 84 good, and from 95 to 100 excellent.

The Knee Osteoarthritis Outcome Score (KOOS) is an extensively used self-administered subjective score (Roos, Roos, Lohmander, Ekdahl, & Beynnon, 1998). KOOS has five subscales; Symptoms, Pain, Activities of Daily Living, Sport and Recreation and Quality of Life, which are interpreted separately with the reference of 100 indicating no symptoms and 0 indicating severe symptoms. The subscales are relevant for a variety of study-populations and follow-up periods. It was originally developed for use in both acute and follow-up phases of knee injury with the perspective that injuries to the meniscus, cartilage and ligaments often lead to knee OA. Validity, reliability and responsiveness is well documented (Paradowski, Bergman, Sundén-Lundius, Lohmander, & Roos, 2006; Roos, Roos, Ekdahl, & Lohmander, 1998).

Activity level

The Tegner Activity Scale (Tegner & Lysholm, 1985) was developed to complement the Lysholm Knee Score. Work, sports and recreation activity is graded on a 1-10 scale. The higher end of the scale reflects activities with pivoting and forceful joint load on a frequent basis (acrobatics, elite soccer, rugby, American football) while activity level 6 and below reflects a more recreational sport (for example recreational downhill skiing) performed less frequently, with less pivoting and less forceful joint loads. Level 1-4 constitutes activities of daily living and work. The instrument can be self-administered but due to possible difficulty of the subjects interpreting the graded levels correct, since one and the same sport can be performed at a greater or a lesser advanced activity level, it has been recommended that the Tegner Activity Scale is assessor-administered as is for our patient group (Frobell, Svensson, Göthrick, & Roos, 2008).

The International Knee Documentation Committee (IKDC) survey is a reliable, valid measure for knee function, symptoms and sports activity (Hefti, Muller, Jakob, & Staubli, 1993; Irrgang et al., 2001; Tigerstrand Grevnerts et al., 2017). It has an objective and a subjective section, and may be freely downloaded at the American Orthopaedic Society for Sports Medicine (AOSSM) website (AOSSM, 2017). For the purpose of this thesis, only the IKDC activity level information was used (study II): The subjects defined their activity level in one of the four IKDC categories Very strenuous (jumping, pivoting, soccer, team handball, floor ball), Strenuous (heavy work, alpine skiing, tennis), Moderate (moderate physical work, running, jogging) and Light (walking, house- or yardwork).

3.6 STATISTICAL ANALYSIS

Descriptive statistics

In all studies, mean (standard deviation or standard error) was reported for the continuous variables which were normally distributed. If data was not normally distributed, this is indicated in the separate studies where median (range or interquartile range) is presented. The Tegner Activity scale is an ordinal scale. It is reported in median (range).

Study I

Comparisons were made with One- and multiway ANOVA. The Lysholm score and the Tegner Activity scale between groups were tested with non-parametric statistics, the Mann-Whitney U-test, due to the ordinal characteristics. For one gait-variable (stance), data was non-normalized and non-parametric statistics was used (the Kruskal-Wallis ANOVA by ranks).

Study II

Differences between injured and non-injured, right/ left leg and sex were tested with Repeated measurements and Oneway ANOVA. A post-hoc Fisher procedure was used to account for multiple comparisons. Further within group differences (sub-analyses) were tested with Student's paired t-test, and between group differences (descriptive data and sub-analyses) with Student's unpaired t-test. Chi-square test (or with small frequencies Fisher's Exact test) was used for testing categorical and ordinal data in contingency tables.

Study III

Patient baseline descriptive data (age, weight, height, BMI and time for injury to surgery) was tested with Student's t-test. Age is shown by mean (range) for clearer description. Primary data was then tested in a General Linear Models ANOVA with repeated measures design for pre- and postoperative comparisons of the healthy and injured leg, and between men and women. Statistic interaction between variables could thereby be pointed out when present. Post-hoc analyses were carried out with Student's t-test. Tegner activity level and KOOS sport and recreation questionnaires were not normally distributed and were separately tested with the Wilcoxon's matched pairs test for the comparison of pre- and postoperative

measurements. Between men and women-comparisons were made with the Mann-Whitney U-test.

Study IV

A power calculation, initially performed for study III, indicated that 30 subjects per group were needed for the randomization into a brace- and non-brace group. The power calculation was based on discovering a 4% decrease in hamstring muscle CSA with 80% power.

Data between groups was tested with Mann-Whitney U-test, Student's unpaired t-test, chi-square or Fisher's exact test (for categorical data). Spearman's rank correlation (ρ ; "rho") was used for correlations. To predict the variables affecting the three-month effusion in the knee joint, we used forward stepwise multivariate logistic regression. In the logistic regression model, we put in the variables age, sex, prior meniscus injury, pre-injury Tegner activity level and baseline Lysholm score.

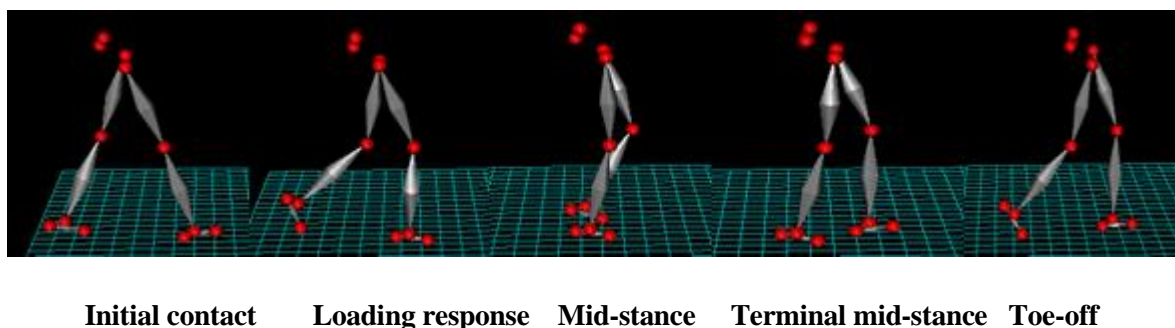
4 RESULTS

4.1 GAIT ADAPTATIONS FOR ACL DEFICIENT COMPARED TO CONTROL SUBJECTS (STUDY I)

Muscular activation

This study of gait mechanics for ACLD subjects and controls, primarily showed significant differences in muscle on- and offset EMG activity for the tibialis anterior (TA) and the lateral gastrocnemius (LG) muscles in and before stance (Figure 4). More specifically, TA onset, before the initial contact, occurred significantly earlier in the healthy leg in the ACLD-group ($p=0.006$) and for the ACLD-group as a whole ($p=0.03$) compared to controls. TA also had a significantly longer duration in the ACLD-group, for the injured leg in the ACLD-group ($p=0.026$) and for the ACLD-group as a whole ($p=0.007$), compared to controls. As the TA was still active, the LG onset in stance occurred in the ACLD-group, significantly earlier for both the injured and healthy legs of the ACL injured group compared to controls ($p=0.03$). The activity pattern resulted in a co-contraction of the TA and LG, which was not seen in the control group. The thigh muscles; vastus medialis (VM) and biceps femoris (BF), did not differ between groups regarding on-/ offset or duration.

Figure 4. Stance of gait.



Gait specifics

There were no significant results for any of the kinematic variables (knee and foot angles in stance and maximum heel-height in swing). There were no primary significant results regarding ground reaction forces from full groups of ACLD or control subjects. Ground reaction forces normalized to body weight showed larger both breaking ($p=0.026$) and propulsive ($p=0.002$) ground reaction forces for woman control subjects, but only when compared to men control subjects. The women as a whole had a significantly longer step length when normalized with body height, but only compared to men ACLD subjects ($p=0.004$). Women from the ACLD group walked faster than men ($p=0.005$), and women had shorter stance time than men in general ($p=0.007$). The latter and the previous two variables may thereby coincide.

4.2 MUSCULAR CSA AFTER ACL INJURY (STUDY II)

The muscular CSA data of this cross-sectional study population was investigated and analyzed for the injured versus the healthy leg, for left injured versus right injured leg and for men and women separately. Further, we compared the CSA in combination of a prior meniscus injury, for different time to surgery and for different activity level before and after injury, but before surgery.

Quadriceps muscle CSA was significantly decreased, or hypotrophied, by 5% in general ($p < 0.001$) compared to the healthy leg. When the injury was in the right leg, the hypotrophy was significantly greater compared with when the injury was in the left leg. ($p < 0.001$). However, when men and women were separated, only women as a group still showed greater quadriceps hypotrophy (CSA ratio injured/ healthy leg) in right-sided injured legs ($p = 0.012$). The hypotrophy for the men was similar for side of injury.

Semimembranosus hypotrophy, loss of CSA, for the injured leg was found for women ($p = 0.026$).

Semitendinosus, gracilis and biceps femoris had a larger CSA ($p = 0.024$, $p = 0.005$, $p = 0.029$ respectively) when the injury was on the right leg.

Meniscus injury, different time to surgery and different activity level did not affect the CSA results after the ACL injury.

4.3 MUSCULAR MORPHOMETRY AND FUNCTIONAL ASSOCIATIONS AFTER ACL INJURY AND RECONSTRUCTION (STUDY III)

The primary outcome variables in this prospective cohort study were muscular CSA and muscular attenuation values. Data was tested with a General Linear Model ANOVA, with repeated measures before and one year after ACLR with a ST/G graft, for the injured and healthy leg.

Muscular CSA and attenuation

Baseline

At baseline the only significant findings were a decreased CSA of the injured leg for the quadriceps (both men and women) as well as for the semimembranosus (only women). In the bicep femoris there was a trend ($p = 0.06$) for an increased CSA for both men and women.

Pre- to postoperatively

Quadriceps did not change from pre- to postoperatively: There was a 5% smaller muscular CSA in the injured leg before the surgery (injured leg), and after one year the difference was the same. Injured leg as a whole, pre- and postoperatively taken together, had significantly smaller CSA ($p < 0.001$). When the injury was in the right leg, CSA was significantly smaller preoperatively compared with when the injury was in the left leg: There was thus a statistical

interaction ($p=0.005$) for the injured versus the healthy leg and the side of ACL injury, meaning that the sides changed differently.

Semimembranosus CSA increased pre- to postoperatively ($p=0.008$), for both legs as seen by the CSA ratio injured/ healthy leg ($p=0.002$). Semimembranosus CSA hypotrophy (injured leg) was present (only for women) before surgery, but not after one year. However, also preoperatively, if the injury was right-sided for men, there was hypertrophy ($p=0.04$) which was not seen when the left and right legs were pooled together. This semimembranosus hypertrophy increased postoperatively in the men for the ACL reconstructed leg ($p=0.01$). And postoperatively, the greater hypertrophy for males which had occurred was no longer dependent on side of injury. The differences may be clearer explained when looking at the patterns of change interactively: The significant different pattern of change from pre- to postoperatively pertaining to the sexes is a statistical interaction ($p=0.033$).

Semimembranosus changed differently for men compared to women, whereas the women started with hypotrophy which hypertrophied to just about equal, while the men started with a bit of hypertrophy, if the injury was on the right side, and they ended up with clear hypertrophy. Statistical interaction was also noted between the injured/ healthy leg for the sexes ($p=0.028$) meaning that the injured versus healthy leg CSA was significantly different, and they were different per sex (men had a larger CSA in the injured leg, and women had a smaller CSA in the injured leg) which also follows from the latter result.

Biceps femoris CSA increased pre- to postoperatively ($p=0.015$), for both sexes.

Preoperatively the CSA was larger for all, but not significantly. At the postoperative measure, there was significant hypertrophy ($p=0.006$) between the ACL reconstructed and the healthy leg for both sexes.

Semitendinosus CSA naturally decreased pre- to postoperatively ($p<0.001$). One of the muscles used for grafting, it was the only one where the CSA did not significantly differ in size between women and men neither before nor after ACLR.

Gracilis CSA naturally (due to grafting) decreased pre- to postoperatively ($p<0.001$). There was a trend towards preoperative hypertrophy when the right leg was injured ($p=0.06$).

Sartorius showed a trend for preoperative CSA hypertrophy but only when the right leg was injured ($p=0.02$).

Attenuation value, or muscle density (HU) decreased from pre- to postoperatively for natural reasons in the muscles used for the ACLR, semitendinosus and gracilis ($p<0.001$ and $p=0.003$ respectively). Quadriceps muscle density was significantly lower both pre- and postoperatively in the injured leg ($p=0.001$). Preoperatively, quadriceps in addition had significantly lower density when the injury was on the right leg, a statistical interaction for injured compared to healthy leg and side of injury ($p=0.03$). After one year, muscle density was lower in quadriceps, semimembranosus and gracilis. Women had lower values in the gracilis, biceps femoris and sartorius compared to men.

Morphometry versus function, activity, scores and clinical tests

Correlations between morphometric data and function showed that one-year quadriceps muscular CSA ratio (injured/ healthy leg) correlated to the one-year hop ratios (injured/ healthy leg) of all four functional hop tests (one-leg hop $p<0.001$, triple-hop $p<0.001$, square-hop $p=0.009$ and 6 m timed hop $p<0.001$). One-year quadriceps attenuation ratio (injured/ healthy leg) was only correlated to the one-year one leg- ($p<0.001$) and the triple hop ($p=0.02$) ratios. One-year postoperative gracilis CSA ratio (injured/ healthy leg), gracilis CSA and gracilis attenuation ratio (injured/ healthy leg) was also positively correlated to the one-year one- and triple hop ratios ($p<0.01$ and $p=0.005$ for CSA ratio, $p=0.02$ and $p=0.01$ for CSA, and $p=0.002$ and $p=0.006$ for attenuation ratio, respectively).

Correlation tests between morphometric data and activity-level and score- variables showed that one-year quadriceps muscular CSA and attenuation ratios (injured/ healthy leg) correlated to one-year Tegner activity level ($p<0.05$). One-year quadriceps muscular CSA ratio (injured/ healthy leg) also correlated to the one-year KOOS sport and recreation subscale ($p=0.04$).

Correlation tests between morphometric data and clinical tests showed that quadriceps attenuation ratio (injured/ healthy leg) correlated positively to one-year heel-height difference ($p=0.04$). Further, one-year gracilis muscular CSA and attenuation ratios (injured/ healthy leg) correlated negatively with side-to-side laxity measures ($p=0.03$ and $p=0.002$, respectively). One-year gracilis ($p=0.04$) and sartorius ($p<0.01$) muscular CSA ratio (injured/ healthy leg) correlated negatively with one-year maximum knee flexion range of motion measures.

Additional general one-year outcome results of the ACL reconstruction

All measured variables (laxity, one-leg hop distance, Lysholm score, KOOS, and Tegner activity level) improved as expected postoperatively. There were outcome differences between the sexes: Postoperative Tegner activity level and KOOS Quality of Life subscale were significantly higher ($p<0.001$ and $p<0.02$, respectively) for men compared to women. Three of four one-year outcome hop ratios were significantly better for men (one-leg hop $p=0.03$, square hop $p=0.02$ and 6 m hop $p=0.002$).

Correlation tests showed that one-year side-to-side knee laxity correlated negatively with the one-year one-leg hop ratio ($p=0.04$). The one-year hop ratios (injured/ healthy leg) for the one- leg hop, the triple hop and the square hop correlated with the one-year maximum knee flexion range of motion measures ($p=0.04$, $p=0.003$ and $p=0.03$, respectively).

4.4 KNEE JOINT EFFUSION AND ITS ASSOCIATIONS BEFORE AND AFTER ACL INJURY AND RECONSTRUCTION (STUDY IV)

This was a prospective, randomized study with parallel group design. Subjects were randomized to wearing or not wearing a postoperative brace, locked in extension while standing and walking for three weeks after ACLR. There were however no significant results between the brace- and non-brace groups, neither for presence of knee joint effusion at three months nor for one-year general outcome variables; the functional hop tests, Lysholm score, KOOS or Tegner activity level. At baseline, 22% of the subjects had presence of knee joint effusion, and there was an association for a prior partial meniscus injury with this presence ($p=0.01$).

Predictors of knee joint effusion three months after ACLR

At three months, 68% of the subjects had presence of effusion. This amount consisted of about 80% of the men and 56% of the women.

The primary variable, presence of knee joint effusion three months after surgery, was significantly associated, via Spearman's correlation, with previous partial meniscus injury, higher Tegner activity level before the injury, male sex and longer time from injury to surgery ($p=0.05$, $p<0.05$, $p=0.05$ and $p<0.05$, respectively). Variables not associated were brace regime, age, BMI, or preoperative Tegner activity level. The variables age, sex, prior meniscus injury, pre-injury Tegner activity level and baseline Lysholm score were then tested with forward step-wise logistic regression in order to determine predictors of presence of joint effusion:

The final logistic regression showed that presence of knee joint effusion at three months after ACLR was significantly associated with partial meniscus injury at baseline ($p=0.05$), a higher Tegner activity level before the injury ($p=0.006$) and there was a trend for association for the Lysholm baseline knee score ($p=0.06$). In a sub-analysis, we found that a previous arthroscopy had no impact on joint effusion at three months, not even if arthroscopy was in combination with a previous partial meniscus injury.

Effect of three-month knee joint effusion on outcome variables one year after ACLR

At one year, 25% of the subjects had presence of effusion. One-year outcome for KOOS sport and recreation subscale was significantly lower for women with presence of effusion compared to men ($p=0.003$).

Women as a whole (with and without effusion) had lower KOOS Quality of Life subscale scores and Tegner activity level compared to men who had effusion at three months ($p<0.01$ for both variables).

Additional general one-year outcome results of the ACL reconstruction

All subjects with effusion at all data collection points were men (11%). They all had Lysholm (>84) and Tegner (>6) outcome score as well as prior partial meniscus injury.

Tegner activity level at one year for men with prior meniscus injury was significantly higher compared to women as a whole and also to men without prior meniscus injury ($p=0.001$).

Shorter injury time before surgery correlated to higher one-year Lysholm score and Tegner activity level ($p<0.05$ for both variables).

Women had lower one-year scores for KOOS sport and recreation subscale, KOOS Quality of Life subscale, Lysholm scores and Tegner activity level, and for one functional hop test, than men (<0.05 , $p<0.01$, $p0.05$, $p=0.001$ and $p<0.01$, respectively).

5 DISCUSSION

In the undertaken projects, gait- and muscular activity adaptations of long-term ACL injured to healthy controls were compared. The effects of an ACL injury on muscular morphometry, effusion and function prospectively were also analyzed in ACL injured and subsequently reconstructed subjects. The findings showed differences in muscular activation patterns in gait of ACLD subjects, side- and sex-dependent differences in muscular morphometry before and after ACL surgery, and possible specific morphometric and functional effects of ST/G grafting. The randomized study demonstrated that postoperative bracing does not have effect on joint effusion. The findings in the studies have also established that meniscus injury and activity level are predictors for joint effusion after ACL surgery, which together with the above findings is of concern for guidelines in rehabilitation.

5.1 GAIT AFTER ACL INJURY

Small but distinct muscular differences of muscles in the lower leg and foot in gait for long-term ACL injured were identified:

First, a possible stability-seeking increased activation time and earlier onset-time was identified for the muscular activity pattern in the tibialis anterior (injured leg) in preparation for and during stance. The findings of the tibialis anterior prolonged duration and earlier activation time before and during stance is in agreement with Ciccotti et al. (1994) who also found increased tibialis anterior muscle activity in gait for ACLD subjects. A study by Binder-Macleod et al. (2006) has in addition found that anterior tibial volume was greater among ACLD patients. It is established that long time rotational tibial adaptations exist in ACLD populations for gait (Andriacchi & Dyrby, 2005; Chaudhari et al., 2008; Zabala, Favre, & Andriacchi, 2015). It may be possible in future research to link the tibialis anterior muscle adaptations in gait to those.

Second, there was an earlier EMG activity from the lateral gastrocnemius comparably, resulting in co-contraction with the tibialis anterior for the ACLD group. Muscular activity patterns of the gastrocnemius, as measured by EMG in our study are thus different between the healthy and ACL injured leg, and also differ from control subjects. Similarly, in a more recent study gastrocnemius activity had a longer duration during a one-leg hop (Klyne, Keays, Bullock-Saxton, & Newcombe, 2012). This correlated significantly to ACLD leg anterior-posterior laxity measures in an ACLD group awaiting ACLR. The present results did not show any associations with knee laxity, but the subjects were coping with the injury and weren't awaiting surgery. The side-to-side laxity values were slightly lower than in the study by Klyne (2012) but the findings may in all suggest that muscular activity in fact is responsible for the adaptation to the injury.

Additional findings of gait specifics in the study were generated partly from differences between women and men (stance-time), and mostly in the sub-groups of women and men in the ACLD and the control group (breaking- and propulsive force, step length and gait speed).

The study was however not designed for gender comparisons and since the sub-group numbers are small, conclusions here would remain uncertain.

Small deviations in gait may be discovered in modern motion analysis, as in this thesis, and researchers are finding additional deviating muscular and joint loading variables for injured and reconstructed subjects, also between the sexes, in other movement tasks as for example landing from a hop or jump (Ford, Myer, & Hewett, 2003; Hewett et al., 2005; Paterno et al., 2010). The results show that compensatory muscle activity patterns do exist, also in copers, even in such an activity of lesser intensity as gait. The effects are still unclear. Adaptations and compensational muscular patterns and their effect on knee joint surface are still pieces in a puzzle, and may take time to sort out. It is suggested that adaptive or altered muscular forces may shift joint loads to other areas (Andriacchi & Dyrby, 2005) or produce greater joint compression force, at least in animals (Herzog et al., 2003). In patients diagnosed with OA, altered hamstring-quadriceps muscle activity balance and adaptive co-contraction is previously documented (Hortobagyi et al., 2005; Hubble-Kozey, Deluzio, Landry, McNutt, & Stanish, 2006; Mills, Hunt, Leigh, & Ferber, 2013). Also, recent research proposes that lowered knee joint moments soon after injury or surgery (but not persisting) may be what causes radiographic OA 5 years after ACLR (Gardinier, Manal, Buchanan, & Snyder-Mackler, 2013; Wellsandt et al., 2016). This shows that it may not only be important to evaluate the size of the moment but also if the found alterations are results of compensatory muscular forces, affecting the joint surface. This underlines the importance of developing and perfecting rehabilitation strategies to attempt to resolve symmetry and muscular activity issues in ACLD and ACLR patients. Research is also needed to specify possible detrimental mechanic patterns and what activities or conditions may result in joint degradation. For example, Tsai et al. (2013) found increased muscle co-contraction for quadriceps and hamstring muscles during a drop landing for women having undergone ACLR. Tibio-femoral joint compression forces were thereby significantly increased. After an intervention of training landing strategies, allowing greater hip- and knee flexion, the muscular co-contractions and joint forces were significantly decreased. The result of the joint forces is based on modelling the muscular forces via EMG, a so called EMG-driven approach, the only possible way to measure force directions and magnitudes as a result of muscle contractions in vivo (Pandy & Andriacchi, 2010).

5.2 MUSCULAR MORPHOMETRY AFTER ACL INJURY AND SURGERY

Further reason for sharpening rehabilitation strategies and patient awareness can be seen from the results from studies II and III. Clearly, there is a need to get musculature ready for satisfactory function, or for possible ACL surgery.

Quadriceps

The 5% quadriceps CSA deficit found in our subjects is unfortunately not unusual in the literature, as mentioned in the introduction. Macleod et al. (2014) specifically studied the quadriceps group with MRI in ACLD subjects. They found that potential copers had decreased vastus lateralis and total quadriceps CSA, and non-copers had decreased vastus lateralis, vastus medialis and total quadriceps CSA. But between the groups, non-copers had less total hypotrophy. Non-copers, compared to potential copers, also had significant hypotrophy in the vastus medialis and vastus intermedius. Further studies are needed for interpreting whether they had hypotrophy in perhaps in a “worse” place than the copers for functional tasks. The copers’ hypotrophy was in the vastus lateralis. The method of the present studies could not separate the individual quadriceps muscles, which was a limitation. Optimally, as determined by MRI studies, CSA at 25 cm above joint line gives the best correlation to muscular volume, but the 15 cm location that we used has good correlation as well (Marcon et al., 2015). At the higher level it may however be easier to separate the muscles.

The new finding of the right leg being more affected by the quadriceps hypotrophy deserves attention. Previous research is scarce. Common belief is that if the manipulating, or kicking leg (most frequently termed as the dominant leg) is constantly used for kicking, there is little doubt that the quadriceps in this leg is more hypertrophic. In the present study population soccer was the most frequent activity but not all subjects were sports active. An MRI study of ten athletes with diverse sports has showed that vastus medialis volume was significantly larger on the dominant side, and vastus lateralis was significantly larger on the non-dominant side (Tate, Williams, Barrance, & Buchanan, 2006). The total quadriceps volume was equal for both sides. It remains unclear why the right side in our study should be more prone to hypotrophy, and perhaps results from the individual quadriceps muscles could have further explained this.

Muscular density of the quadriceps, as determined by CT attenuation measures, was decreased both before and after ACLR without a change pre- to postoperatively. It was preoperatively decreased more if the injury was on the right side. In studies of CSA and muscle density before and at time-points after total hip replacement, Rasch et al. (2009) found that muscle density recovered slower than CSA. For healthy men it took seven weeks to recover total quadriceps CSA and vastus lateralis density from four weeks of unloading (Berg et al., 1991). Muscle tissue quality and its associations to function, BMI/ body weight and strength have so far been fairly unexplored for ACL injured populations. In a community-population, a decreased fatty infiltration of the vastus medialis musculature was

associated to less cartilage thinning in the medial tibia and patella (Teichtahl et al., 2015). The importance of the quadriceps for physical function are emphasized by the present muscle density findings, which also correlate to the same variables as the quadriceps CSA; the functional hop tests (although not all), and the activity level.

The present results showed that quadriceps was the major affected muscle for CSA and density (negatively affected both before and after ACLR). It is therefore important to discuss the possible influence of quadriceps inhibition after injury and surgery. AMI; neuromuscular activation deficits, pain and effusion, may cause “delay” of proper muscular CSA, density and strength development. This may also explain why structured pre-conditioning after ACL injury but before surgery has not contributed to increased quadriceps CSA four weeks after ACLR (Grapar Zargi, Drobic, Vauhnik, Koder, & Kacin, 2017) or increased quadriceps muscle volume 12 weeks after ACLR (Shaarani et al., 2013). Neuromuscular voluntary quadriceps activation deficits may also be bilateral (Harkey et al., 2016; Konishi, Aihara, et al., 2007). Thus, although not investigated within the scope of this thesis, another obstacle in rehabilitation on top of the hypotrophy seems to be diminished output quality of quadriceps muscle activation. After six months CSA was found to correlate well to quadriceps strength (Thomas et al., 2016). Quadriceps strength was however not restored that early after ACLR and was only 70% of the healthy leg. CSA was decreased by 15%. The authors however concluded that they believe negative effects from AMI at that time finally had diminished. This was also shown in the neuromuscular research by Harkey et al. (2016), who used stimulus to the femoral nerve for evaluating spinal reflexes. Interestingly, neuromuscular activation deficiency in the hamstrings does not seem applicable in ACL injured and reconstructed subjects. Peak torque (tested isokinetically) per unit muscle volume (evaluated by MRI) does not seem affected by ACL injury (Konishi, Kinugasa, et al., 2012). Twelve months after ACLR, testing provided a significantly lower peak torque per muscle unit volume bilaterally, compared to controls (Konishi & Fukubayashi, 2010). However, the authors found no evidence for neuromuscular recruitment deficiency.

The present one-year results of both quadriceps hypotrophy and lower muscular density correlated with worse KOOS-scores (Sports and Recreation), and also include a subject profile with a lower Tegner activity level. The present studies did not include strength tests, but investigations which compare strength and subjective function agree with the association between decreased strength and lower subjective function, (D. Logerstedt, Lynch, Axe, & Snyder-Mackler, 2013; Pietrosimone et al., 2016). Quadriceps strength and objective function, hop tests, have a prior established association (Keays 2003 och Schmitt 2012) which is also interpreted in the present study results of quadriceps CSA and muscular density.

Semimembranous and biceps femoris

Differences preoperatively and over time in the semimembranosus CSA were dependent on sex. This finding is interesting since sex differences for hamstring activation are found also in healthy activity performance of for example drop landings (Chappell, Creighton, Giuliani, Yu, & Garrett, 2007). Women also tend to engage hamstrings to a lesser extent than men, and

depend more on their quadriceps (Krishnan, Huston, Amendola, & Williams, 2008). The preoperative semimembranosus hypotrophy for women may thus be anatomically and biomechanically constituted, where women in general habitually and in sport activity rely less on the medial hamstring group. The postoperative semimembranosus hypertrophy in the ACLR leg of men may along the same thoughts be compensatory. MRI studies have shown that semimembranosus hypertrophy is significantly greater in subjects where the semitendinosus tendon does not regenerate well (Eriksson et al., 2001). A compensatory rationale may also be used for the biceps femoris which hypertrophied in general over time. The present indications of preoperative hypertrophy for the bicep femoris when the injury occurred on the right side is new information, and should perhaps be interpreted together with the significant right-sided preoperative hypotrophy of the quadriceps CSA. Williams and colleagues (Williams et al., 2005) has investigated muscle volume for the biceps femoris but had non-significant results preoperatively. One reason may have been that measurements occurred a shorter time from injury, only three months, whereas our population was on average 24 months from injury.

Semitendinosus and gracilis

Semitendinosus was the only muscle where CSA did not differ between the sexes neither pre- nor postoperatively. It would therefore not have been surprising if this muscle had been singled out as more important for function involving women. Instead, the one-year gracilis CSA, CSA ratio and CSA attenuation ratio injured/ healthy leg correlated negatively with two of four hop tests. This was together with the quadriceps CSA hypotrophy, which correlated with all hop tests, and the quadriceps CSA attenuation ratio injured/ healthy leg, which correlated with two of the hop tests. The gracilis also correlated negatively with side-to-side laxity, and taken together this signals a negative consequence from the harvesting of the medial tendons. Functionally, loss of the internal tibia rotators (in the present case also including the lack of hypertrophy in womens' semimembranosus) causes diminished internal rotation torque (Viola, Sterett, Newfield, Steadman, & Torry, 2000). For women this torque hasn't recovered after 12 months (Segawa et al., 2002) which may be important for the hop-tasks. However, we speculate that the findings of compensatory hypertrophy of the biceps femoris and semimembranos (for men) to an extent may counteract the functional deficits. Further, the sex difference in hop function (women had lower one-year hop ratios than men) could explain some of the significantly decreased subjective scoring and activity level for women, who do tend to be less satisfied in subjective follow-up after ACLR (Ageberg et al., 2010; Paradowski et al., 2006). It is not within the scope of this thesis to specifically evaluate the surgery harvest site. A systematic review from 2015 (Suijkerbuijk, Reijman, Lodewijks, Punt, & Meuffels, 2015) however reports that the harvested tendons regenerate in about 70% without differences between the sexes, but that function and strength relationships remain unclear due to lack of research.

5.3 EFFUSION AFTER ACL INJURY AND SURGERY

Effusion after injury and surgery is another obstacle which usually precedes knee well-being. As seen above in the discussion pertaining to the quadriceps, there is evidence that AMI (thus also effusion) may interfere with quadriceps neuromuscular pathways, that it prevents adequate muscular activation, and that this may have bilateral effect.

The most important, the predictive, variables for presence of effusion at three months were a prior partial meniscus injury and a higher Tegner activity level before the injury, along with a higher Lysholm score before the injury. The profile for the subject with the three-month effusion may be one who is fairly active and who may be using their injured leg in a more carefree manner also after injury and surgery. The association between meniscus injury and effusion is strong also at baseline. It could possibly also be the *person* with the meniscus injury who is providing the risk for that association: Men in the present study with a prior meniscus injury also have higher Tegner activity level at one year, compared both to men without a prior meniscus injury and to women as a whole. Interestingly, the six subjects who had presence of effusion at all measuring points did have a prior partial meniscus injury, and at baseline and 12 months a fairly high Lysholm score (>84) and Tegner level (>6), and they were all men. Prior arthroscopy did not influence the results neither at baseline nor at three months postoperatively.

The present new result is important: Effusion is still present in 68% of the subjects at three months and is slightly worse than preoperative levels also one year after surgery (25%). Also at baseline, a prior meniscus injury correlated to presence of effusion. It is well known that concomitant meniscus injuries predispose for OA (Claes et al., 2013; Culvenor et al., 2013). From the present results it is not possible to draw conclusions for associations to OA from the presence of effusion, but it is clear that such investigations must take prior partial meniscus injuries into account. Further, it is established that effusion may linger in populations of OA patients but not all are affected (Cattano et al., 2011). Different biochemical components in joint fluid between subjects may signify that the presence of effusion may be individually different. Therefore the authors suggest that individuals with OA should be further investigated within the respective subgroups (Cattano et al., 2011).

5.4 BRACING AFTER ACL SURGERY

Bracing was a primary variable in follow-up for possible effects on presence of effusion at three months after ACLR, and in long-term follow-up (one year). In previous randomized studies, general outcome of postoperative bracing has been investigated only for subjects with a PT graft (Brandsson et al., 2001; Harilainen & Sandelin, 2006; Möller et al., 2001; Risberg, Holm, Steen, et al., 1999). Results from previous studies have so far been generalized to be true also for ACLR patients with an ST/G graft. With the results from the present research, we have now verified that there is no apparent role for postoperative bracing after ACLR with ST/G graft: In study IV, the postoperative brace regime after ACLR did not prevent presence of effusion at three months. Neither did it have any effect in one-year clinical functional or

subjective follow-up variables. In study III, there were no significant associations from bracing in one-year follow-up of clinical, subjective and functional variables or for muscular CSA. However, the specific primary variable of bone tunnel enlargement after ACLR with an ST/G graft has been tested in a randomized study (Vadala et al., 2007). The subjects were randomized to a brace group without range of motion for two weeks, or to a non-brace unrestricted group. After 10 months, there was significant bone tunnel enlargement in both groups, and significantly more enlargement in the non-brace group compared to the brace group. No other clinical outcome result other than range of motion was investigated.

5.5 ASPECTS ON CLINICAL OUTCOME OF ACL SURGERY

Sex differences

Both study III and IV has revealed some important sex-related differences in one-year outcome of ACLR. These are not yet studied in depth in the literature. In both studies women had lower subjective one-year outcome scores, which confirm the results of previous authors (Ageberg et al., 2010; Paradowski et al., 2006) as mentioned in the *Semitendinosus and gracilis* section above. Further, the women with and without effusion at three months in study IV had lower subjective scores and Tegner activity level compared to men, and also compared to men with effusion. This may emphasize women's general dissatisfaction. Authors of a recent meta-analysis (Tan, Lau, Khin, & Lingaraj, 2016) report that women have inferior instrumented laxity results, but they do not achieve inferior objective functional hop test results compared to men. Women's subjective scoring together with the lower functional hop ratios injured/ healthy leg (three of four hop-tests in study III and one in study IV), as well as lower Tegner activity (study III and IV) and Lysholm scores (study IV) in our study population may however be related to some of the lesser developed musculature after ACLR. The lack of compensatory hypertrophy in the semimembranosus compared to the men was discussed in the *Semimembranosus and biceps femoris* section above. Women also had less postoperative muscle density in the gracilis, sartorius and biceps femoris. This combination of conditions in the medial muscle/ tendon complex could be causing the serious set-backs for the objective, and thereby subjective, function for these women.

General outcome

Generally, for women and men combined in this study population, laxity correlated negatively with one-year hop ratios (injured/ healthy leg; study III). Laxity and hop test results has previously been discussed due to the association with gracilis muscular morphometry, in the *Semitendinosus and gracilis* section above. The negative gracilis muscular function influence on knee-stability and muscular function, and thereby the negative aspects of using gracilis for grafting, cannot be overlooked in this study population.

5.6 GENERALIZABILITY OF RESULTS: STUDY SAMPLE VERSUS GENERAL ACL POPULATION

The individuals with chronic ACLD subjects in study I had been seen at the orthopedic clinic for the ACL injury, well before recruitment, and were not complaining about their knee at the time of recruitment or the investigation. They had not asked for ACL reconstructive surgery, and are considered as a generalized medium-active sample of individuals with this type of injury. There were 62% men, which is fairly comparable to the regular incident rate in Sweden of about 60% (Nordenvall et al., 2012). The ACLR sample can also be generalized to the ACLR sample of the Swedish population on account of age and male – female proportion, according to the Swedish National ACL register (Nordenvall et al., 2012). According to the authors, ACL reconstruction in Sweden is performed in 36 % of ACL injured men and 37% of the women. It is however important to note that the studied ACLR population is not as homogeneous as, for example, an elite athletic population in a specific sport. However, Tegner activity levels prior to the ACL injury were on the high end; 70% had pre-injury Tegner activity level of 7 or higher, with narrow ranges.

The KOOS is widely used for knee injured populations, it is one of the recommended instruments for ACL-injured populations (Collins, Misra, Felson, Crossley, & Roos, 2011) and it does have reference norms. The studied ACLD subjects, who were copers, had lower scores for the two compared subscales of KOOS Sport and Recreation and the KOOS Quality of Life than age matched healthy subjects (Paradowski et al., 2006). However, the studied ACLD subjects scored higher than the Swedish population of ACL injured about to undergo ACLR, according to data from the National Swedish ACL register (Kvist et al., 2014). The present ACLR population was similar regarding the baseline KOOS score, but one year postoperatively the studied population was more satisfied in general in comparison with the results from the National Swedish ACL register (Kvist et al., 2014).

5.7 METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

General considerations

In study I, there was a wide range in years in time since injury for the ACLD subjects. On one hand the study is strengthened by the fact that the lower range included no patients with less than a year since injury, but on the other hand a limitation is that there was a high upper limit for the range. Confounding factors such as periodically increased pain or an “on-off” sensation of knee well-being may affect the primary variables of gait. A narrower upper range limit would also consider inclusion not being biased by the development of further meniscal or chondral injury and OA. However, as discussed in study I, those with longer time from injury were equally satisfied with their knee.

Another limitation for study I arose in the movement analysis. When skin markers are less than three on each segment, as in the research method in this thesis, there's limitation to what data output can yield. Mathematic formulae cannot be applied with ease to locate joint centers, and if joint centers aren't appropriately located, joint moment information cannot be

reported. Such information could have facilitated data interpretation and made data from other research more comparable.

In study II and III, CT was used for CSA measurements at a predetermined distance from the knee joint instead of, for example, mid-thigh. This did not take into consideration individual bone length or height difference of individuals, and may make the data points less related. However, as mentioned in the discussion, CSA measurements show good correlation to total muscular volume both 15 and 25 cm above the joint line (Marcon et al., 2015), and we used 15 cm in study II and III. Another limitation was the inability of separating the vastii group of the quadriceps muscle. A more proximal measurement such as 25 cm above joint line may have allowed this (Marcon et al., 2015). Finally, in study II and III inferences are drawn about preoperative hypo-/ hypertrophy and muscle density. In fact, we cannot know what the precise condition of the muscles was before the injury, since normative data is missing in the literature.

Some general confounding factors are difficult to account for when assessing findings from the ACLR cohort: We cannot account for differences in individual compliance with exercise, regime or differences of effort in rehabilitation, or psychological aspects of the injury. These factors may affect short as well as long-term outcome. Scores like the EQ5D, a health-related quality of life-score (EuroQol, 1990) indicate how subjects perceive their general health, from very bad to good, and could have appropriately added to the one-year outcome interpretation. The SF-36 (Sullivan, Karlsson, & Ware, 1995), another patient-reported health-related quality of life instrument, could have indicated whether pain or depression explained lower subjective knee function ratings, like those of women's lower one-year KOOS Quality of Life subscale scores. The EQ5D and the SF-36 were collected in the ACLR population, but were not administered from the very start of the project and could thus not be appropriately analyzed. Further, long-term follow-up naturally poses the problem of possible life-style change, due to the injury or other personal reasons.

Another methodological consideration for both the ACLD and the ACL injured and subsequently reconstructed cohort is the absence of strength measurements for knee extension and flexion. Such measurements could have given interesting information of possible associations of EMG, CSA and muscle density, even though isolating muscle mass in strength testing is difficult. In future studies, such an approach could provide further knowledge and thus clinically very relevant information.

Statistical considerations

Study I

We analyzed means of five walking trials, which enhances methodological precision. Despite that, a limitation of the study is that a much larger subject sample would have been needed, as discussed in study I, for detecting small but perhaps important significant deviations of gait data. For example, to test with adequate statistical power for significant difference between

the reported knee angles of the groups of healthy and ACLD subjects, 150 subjects for each group would have been needed. Further, sex differences, due to the smaller sample size, cannot be adequately discussed in our population.

Study II and III

Small samples in subgroups made results less reliable for the analysis of injured/ non-injured left and right leg comparison between men and women. The absence of a control group further enhances this limitation.

Study IV

The power calculation for the ACLR group for the randomization procedure was based on the primary outcome variable of muscular CSA. However, the subject sample was generally small for primary statistically tested variables (logistic regression) and normality-analyses, and this makes preclusions difficult especially in subgroups. Non-parametric statistics were used due to non-normality. Finally, the p-values are descriptive values, and in this type of statistics do not take into account the amount of multiple comparisons.

5.8 CONCLUSION AND CLINICAL IMPLICATIONS

The aims of this thesis lie within a frame of research which seeks small but possibly, in the long run, important deviations or deficits in ACL-injured and reconstructed individuals. This has substantial implications both regarding joint stability and future development of OA. The presented results have many individual components to consider for the clinician, for the ACL injured and reconstructed patient and for future research.

Gait

Lower leg and foot muscle activity patterns differ in longtime injured chronic ACL injured subjects compared to healthy control subjects: There is a possible stability-seeking increased tibialis anterior activity time, as well as earlier muscle onset beginning before stance. In combination, there is co-contraction of the gastrocnemius/ tibialis anterior provided by earlier gastrocnemius muscle activity onset. The findings may add to further understanding in the important research of muscular and joint mechanics after ACL injury.

Clinical implication and future perspective

Even though gait and basic movement may seem symmetric in the eye of the clinician, muscular deviations may exist. Clinician sensitivity in assessing and designing rehabilitation is recommended. EMG should be used for comprehensive movement analysis in this type of research.

Muscular CSA and attenuation

Decreased quadriceps muscular CSA (hypotrophy) and density deficits exist before and one year after ACLR, and a right leg injury is more affected before surgery. The right leg injury also has a possible compensatory greater CSA before the surgery, a hypertrophy, in flexor-/internal rotator muscles (in study II the gracilis, semitendinosus and biceps femoris, and in study III the semimembranosus, for men). Increased CSA or hypertrophy in the biceps femoris muscle, which is generally present before the ACLR, is more robust after one year. Clear sex differences exist for CSA pre- and postoperatively for mainly the semimembranosus muscle, which is hypotrophied in women before ACLR, and hypertrophied in men after ACLR. Prior meniscus injury, time from injury or activity level before the injury doesn't influence preoperative morphometry. Not surprisingly, quadriceps CSA and attenuation (density) values have a dominant role in associations with functional hops, subjective scores and activity level after surgery, and this also coincides with generally lower postoperative outcome scores for women.

Clinical implication and future perspective

Rehabilitation and assessment after injury and surgery with extra respect to sex and side of injury is warranted, due to differences in muscular appearance after injury and surgery. The knowledge is clearly applicable when designing rehabilitation. Future research attention should focus on the detailed muscular differences between the sexes, and normative data should be established.

Effusion

Almost 70% of ACLR subjects have not reached knee homeostasis regarding knee joint effusion three months after surgery. A previous meniscus injury and a high activity level before ACL injury are main predictors of this effusion.

Clinical implication and future perspective

Knee joint effusion is a severe clinical sign. Patients with previous meniscus injury should be expected to achieve knee homeostasis, and thus possibly readiness, for full muscular activation and force later in the rehab process than those without previous meniscus injury. The perspective on what curbs effusion (after ACL injury and surgery) and the perspective of effusion on future OA must be evaluated in the future.

ACLR prospective- and outcome differences between the sexes

After the ACLR, male outcome results of functional hop tests, activity level and subjective scores are better compared to female results. The over 50% women, who also had effusion at three months after surgery, score "worst of the worst" in subjective scores. This is despite the fact that far more men, proportionally, have effusion at three months. Taken together, surgery outcome results clearly indicate that there are differences in muscular, functional and subjective response to injury and surgery between the sexes.

Clinical implication and future perspective

Rehabilitation protocols for men and women should reflect differences in the muscular response to injury and surgery. The difference in anatomical predisposition may need additional research consideration. Further investigations on reasons for women's lower subjective scoring are needed.

Postoperative bracing

Bracing doesn't prevent effusion, nor does it affect one-year outcome variables after ACLR with an ST/G graft.

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